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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**U.S. Patent No. RE38,551 (Reissue of U.S. Patent No. 5,773,475)**
Inventor:	KOHN, Harold
Original Issue Date:	June 30, 1998
Reissue Issue Date:	July 6, 2004
For:	ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES
Assignee:	Research Corporation Technologies, Inc.
Date:	December 23, 2008
Attorney Docket:	32555-0002-3
NDA:	**NDA 22-254 (VIMPAT® injection)**

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL FOR APPLICATION FOR EXTENSION OF PATENT

Sir:

Transmitted herewith for filing is an Application For Extension of Patent Term Under 35 U.S.C. §156 with respect to the above-identified patent.

Applicant, the assignee of the above-referenced patent, on this day has filed simultaneously four related applications for extension of patent term under 35 U.S.C. §156, including the present application referenced in the header above. These four patent term extension applications relate to different combinations of U.S. Patent nos. Re38,551 and 5,654,301 and FDA approvals for New Drug Application nos. NDA 22-253 and NDA 22-254. The four patent term extension applications are summarized in the following table.

Attorney Docket No.	Patent No.	NDA No.	Approved Product
32555-0002-1	Re38,551	NDA22-253	VIMPAT® (lacosamide) tablet
32555-0002-2	5,654,301	NDA 22-254	VIMPAT® (lacosamide) injection
32555-0002-3	Re38,551	NDA 22-254	VIMPAT® (lacosamide) injection
32555-0002-4	5,654,301	NDA 22-253	VIMPAT® (lacosamide) tablet

Applicant asserts that it has the right, under 35 U.S.C. § 156, to extend two patents relating to VIMPAT® (lacosamide) because two NDAs, NDA 22-253 and NDA 22-254 for VIMPAT® (lacosamide) tablet and VIMPAT® (lacosamide) injection, respectively, were approved on the same day, namely October 28, 2008, and because there were no approvals of lacosamide that occurred prior to October 28, 2006. As such, Applicant has submitted the above four applications for patent term extension with the goal of ultimately obtaining one patent term extension for each of U.S. Patent nos. Re38,551 and 5,654,301.

Applicant respectfully requests that if the Commissioner determines that both of U.S. Patent nos. Re38,551 and 5,654,301 are entitled to a patent term extension under the same regulatory review period or periods (i.e., for the same NDA(s)), and/or determines that at least one of U.S. Patent nos. Re38,551 and 5,654,301 is entitled to a patent term extension under both regulatory review periods (i.e., for both of the two NDA approvals), that the Commissioner establish a time period in accord with the policies set forth in MPEP § 2761 within which the Applicant will be permitted to elect the patent and product combination(s) for which extension is desired and/or to voluntarily withdraw applications. At that time, Applicant will elect and withdraw applications for patent term extension, as appropriate, to ensure that only one patent is extended for each NDA, and such that a given patent obtains only one extension under 35 U.S.C. § 156.

Applicant respectfully requests that if the Commissioner does not share Applicant's view that it is entitled under 35 U.S.C. § 156 to extend a different patent for each of the two above-identified simultaneously-approved NDAs, that the Commissioner direct the Office to contact the undersigned attorney.

In light of the above, and in accordance with the requirements of 35 U.S.C. § 156, attached for the patent and NDA approval identified in the above header are the following:

1) Application For Extension of Patent Term (including Exhibits A-F) – application 14 pages and Exhibits 121 pages for 135 pages total;

2) Extra copy 1 of Application for Extension of Patent Term (including Exhibits A-F) – application 14 pages and Exhibits 121 pages for 135 pages total; and

3) Extra copy 2 of Application for Extension of Patent Term (including Exhibits A-F) – application 14 pages and Exhibits 121 pages for 135 pages total.

☒ Please charge my Deposit Account No. 50-1349 the amount of $1,120.00, which is believed to be the appropriate fee for a patent term extension as established by 37 C.F.R. § 1.20(j),.

☒ The Commissioner is hereby authorized to charge payment of any fees associated with or necessary for the prosecution of this patent term extension application, including debiting any deficit or crediting any overpayment relating to the fee identified above, to Deposit Account No. 50-1349.

Respectfully submitted,

HOGAN & HARTSON LLP

Dated: December 23, 2008

By: _____
Kevin G. Shaw
Registration No. 43,110

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	**U.S. Patent No. RE38,551 (Reissue of U.S. Patent No. 5,773,475)**
Inventor:	KOHN, Harold
Original Issue Date:	June 30, 1998
Reissue Issue Date:	July 6, 2004
For:	ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES
Assignee:	Research Corporation Technologies, Inc.
Date:	December 23, 2008
Attorney Docket:	32555-0002-3
NDA:	**NDA 22-254 (VIMPAT® injection)**

Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF PATENT

TERM UNDER 35 U.S.C. §156

Commissioner for Patents:

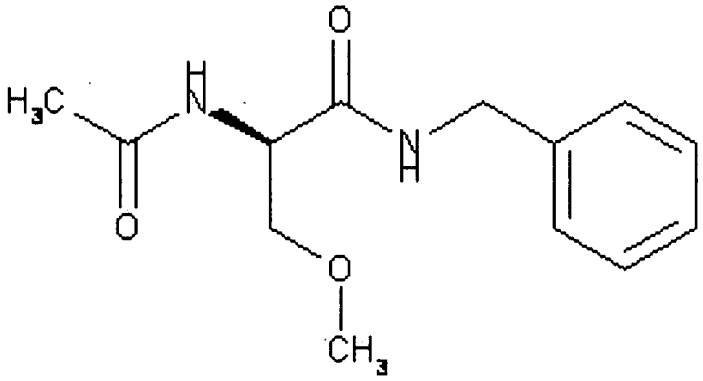
Applicant, Research Corporation Technologies, Inc., a non-profit corporation organized and existing under the laws of Delaware, and having a principal place of business at 5210 E. Williams Circle, Suite 240, Tucson, Arizona 85711-4410, represents that it is the owner of the entire interest in and to U.S. Patent No. Re38,551, granted to Harold Kohn for "Anticonvulsant Enantiomeric Amino Acid Derivatives," as reflected in the assignment document recorded by the U.S. Patent and Trademark Office on May 22, 1997 at Reel 008538, Frame 0093. Attached at **Exhibit A** is a Power of Attorney document appointing the undersigned patent attorney as legal representative of Applicant.

Schwarz Biosciences, Inc. ("Schwarz"), a corporation of the state of Delaware and having a place of business at 1209 Orange St., Wilmington, DE 19801, is the owner of a New Drug Application ("NDA") for VIMPAT® injection, NDA number NDA 22-254. Schwarz Pharma AG ("SPAG"), having its registered office at Alfred-Nobel Strasse 10, 40789 Monheim, Germany, has exclusive license rights under U.S. Patent No. Re38,551 to lacosamide, R-2-Acetamido-N-benzyl-3-methoxypropionamide. Schwarz and SPAG are related companies, being wholly owned by UCB S.A., which has its registered office at Allée de la Recherche 60, 1070 Brussels, Belgium. Attached at **Exhibit B** is a Letter of Reliance document granting the Applicant from Schwarz Biosciences, Inc. the right to rely upon NDA 22-254 and the activities of SPAG and its predecessors in interest supporting FDA approval of VIMPAT® injection for purposes of obtaining any and all patent term extensions available in conjunction with the approval of VIMPAT® injection.

Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156, based upon the approval by the Food and Drug Administration for commercial marketing or use of VIMPAT® injection, since the active ingredient of VIMPAT® injection is lacosamide and lacosamide falls within the ambit of the claims of U.S. Patent No. Re38,551. The information contained in this Application and its Exhibits is provided in accordance with the rules promulgated by the U.S. Patent and Trademark Office at 37 CFR §§1.710-1.785 and presented in the manner set forth at 37 CFR §1.740.

1. A Complete Identification Of The Approved Product As By Appropriate Chemical And Generic Name, Physical Structure Or Characteristics

The approved product, VIMPAT® injection, contains lacosamide as its active ingredient and is indicated for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible. The IUPAC chemical name of lacosamide is (R)-2-acetamido-N-benzyl-3-methoxypropionamide. Lacosamide has the empirical formula $C_{13}H_{18}N_2O_3$, and has a molecular weight of 250.30. Lacosamide is present in VIMPAT® injection in the form of its single (R)-enantiomer, and has the structural formula:



Lacosamide is prepared as a white to light yellow powder that is sparingly soluble in acetonitrile and ethanol. The approved product is formulated for intravenous injection as a clear, colorless, sterile solution containing 10 mg lacosamide per mL for intravenous infusion. One 20 mL vial contains 200 mg of lacosamide, plus inactive ingredients sodium chloride and water for injection. Hydrochloric acid is used for pH adjustment, giving VIMPAT® injection a pH of 3.5 to 5.0. The initial recommended dosage regimen is 100 mg of lacosamide infusion per day, and dosage can be increased, such as at weekly intervals of 100 mg/day, until a maintenance dose of 200 to 400 mg/day (based upon individual patient response and tolerability) is reached.

2. A Complete Identification Of The Federal Statute Including The Applicable Provisions Of Law Under Which The Regulatory Review Occurred

The approved product, VIMPAT® injection, was subject to regulatory review under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355).

3. An Identification Of The Date On Which The Product Received Permission For Commercial Marketing Or Use Under The Provision Of Law Under Which The Applicable Regulatory Review Period Occurred

The approved product, VIMPAT® injection, received permission for commercial marketing or use under Section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. §355) on October 28, 2008. A copy of a letter from the Food and Drug Administration ("FDA") indicating the date of approval is attached hereto at **Exhibit C**.

4. In The Case Of A Drug Product, An Identification Of Each Active Ingredient In The Product And As To Each Active Ingredient, A Statement That It Has Not Been Previously Approved For Commercial Marketing Or Use Under The Federal Food, Drug, and Cosmetic Act, The Public Health Service Act, Or The Virus-Serum-Toxin Act, Or A Statement Of When The Active Ingredient Was Approved For Commercial Marketing Or Use (Either Alone Or In Combination With Other Active Ingredients), The Use For Which It Was Approved, And The Provision Of Law Under Which It Was Approved

The active ingredient in VIMPAT® injection is lacosamide, which has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

5. A Statement That The Application Is Being Submitted Within The Sixty Day Period Permitted For Submission Pursuant to 37 CFR §1.720(f) And An Identification Of The Date Of The Last Day On Which The Application Could Be Submitted

This application is being submitted within the permitted sixty (60) day period, the last day of which is December 26, 2008.

6. A Complete Identification Of The Patent For Which An Extension Is Being Sought By The Name Of The Inventor, The Patent Number, The Date Of Issue, And The Date Of Expiration

The complete identification of the patent for which extension is sought is:

Inventor:	Harold Kohn
Patent Number:	Re38,551 (a Reissue of U.S. 5,773,475)
Issue Date of U.S. 5,773,475:	June 30, 1998
Expiration Date:	March 17, 2017 (without extension under 35 U.S.C. §156)

7. A Copy Of The Patent For Which An Extension Is Being Sought, Including The Entire Specification (Including Claims) And Drawings

A complete copy of U.S. Patent No. Re38,551 is annexed as **Exhibit D**.

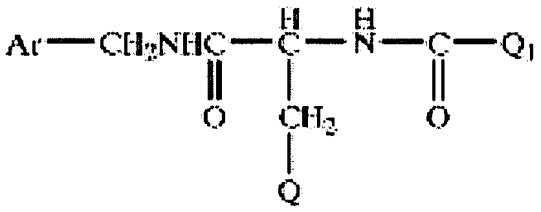
8. A Copy Of Any Disclaimer, Certificate of Correction, Receipt Of Maintenance Fee Payment, Or Reexamination Certificate Issued In The Patent

The patent for which extension is being sought has not been the subject of any disclaimer, certificate of correction, or reexamination certificate. The first maintenance fee was

duly paid on September 28, 2001 by Applicant (for U.S. Patent 5,773,475), and the second maintenance fee was duly paid on November 23, 2005 by Applicant, and the next maintenance fee is due to be paid by December 31, 2009. No additional maintenance fees are due at this time. Copies of the maintenance fee statements evidencing this status are annexed as **Exhibit E**.

9. A Statement That The Patent Claims The Approved Product Or A Method Of Using Or Manufacturing The Approved Product, And A Showing Which Lists Each Applicable Patent Claim And Demonstrates The Manner In Which At Least One Such Patent Claim Reads On The Approved Product Or Method Of Using Or Manufacturing The Approved Product

U.S. Patent No. Re38,551 claims the approved product, VIMPAT® injection. More specifically, claims 1-5 and 7-9 read on the approved product and claim the active ingredient of the final approved product lacosamide, claim 10 reads on the approved product and claims a therapeutic composition comprising lacosamide, and claims 11-13 read on methods that comprise using lacosamide for treatment of central nervous system disorders. Claim 1, covering a compound, is compared to the approved product in the table below.

Patent Claim	Approved Product
1. A compound in the R configuration having the formula:  wherein Ar is phenyl which is unsubstituted or substituted with at least one halo group; Q is lower alkoxy, and Q_1 is methyl.	The active ingredient of the approved product is lacosamide, which is (R)-2-acetamido-N-benzyl-3-methoxypropionamide. Lacosamide has an R configuration, and has the structural formula identified above in Section 1 of this application. Comparison of the structural formula above with that in claim 1 shows that the benzene ring at the far right of the structure in Section 1 satisfies the unsubstituted phenyl "Ar," the $-OCH_3$ group at the bottom satisfies the lower alkoxy "Q," and the $-CH_3$ group at the far left of the structure in Section 1 satisfies the methyl "Q_1."

Claim 10, covering a therapeutic composition, is compared to the approved product in the table below.

Patent Claim	Approved Product
10. A therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims 1-9 and a pharmaceutical carrier therefor.	The active ingredient of the approved product is lacosamide, and lacosamide falls within the scope of claim 1 as indicated above. The approved product is a composition that contains lacosamide present in inactive ingredients sodium chloride in water, making the composition suitable for injection. Sodium chloride and water qualifies as a pharmaceutical carrier.

Claim 11, covering a method of treating central nervous system disorders, is compared to the approved product and its indicated use in the table below.

Patent Claim	Approved Product
11. A method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of claims 1-9.	The active ingredient of the approved product is lacosamide, and lacosamide falls within the scope of claim 1 as indicated above. Lacosamide is an anticonvulsant approved for the treatment of partial-onset seizures in patients with epilepsy, which is a central nervous system disorder.

10. A Statement, Beginning On A New Page, Of The Relevant Dates And Information Pursuant To 35 U.S.C. § 156(g) In Order To Enable The Secretary Of Agriculture, As Appropriate, To Determine The Applicable Regulatory Review Period As Follows (i): For A Patent Claiming A Human Drug Product, Antibiotic, Or Human Biological Product, The Effective Date Of The Investigational New Drug (IND) Application And The IND Number; The Date On Which A New Drug Application (NDA) Or A Product License Application (PLA) Was Initially Submitted And The NDA Or PLA Number And The Date On Which The NDA Was Approved Or The Product License Issued

Schwarz Biosciences, Inc. was notified via telephone that the IND for VIMPAT® injection (IND 68,407) became effective on November 14, 2003, and received a letter dated December 24, 2003 from the FDA confirming that IND 68,407 became effective on that earlier date. For purposes of this application for patent term extension, the Applicant is entitled to an IND date of at least as early as November 14, 2003.[1] The NDA (NDA 22-254) for VIMPAT® injection was initially submitted to the Food and Drug Administration on September 28, 2007 and was approved on October 28, 2008.

[1] A predecessor in interest to Schwarz, Harris FRC Corp., previously filed IND 57,939 for VIMPAT® (lacosamide) tablet. IND 57,939 became effective on May 19, 1999, and was followed by NDA 22-253 on September 28, 2007. NDA 22-253 was approved on October 28, 2008 for VIMPAT® (lacosamide) tablet. Both NDA approvals (for NDA 22-253 and NDA22-254) rely upon the same Phase I safety & tolerance studies for lacosamide. (See Exhibit F, page 1 for "IND 68,407 Submissions" chart indicating on October 15, 2003 a cross-referencing was made to "all preclinical and clinical reports from oral IND"). Applicant understands that, where multiple INDs are in effect, and data from such multiple INDs was material to the determination to approve the product, it is the policy of the FDA to consider whether it would be appropriate to define the testing phase as having begun when the first IND became effective. Applicant therefore submits that an earlier IND effective date, namely May 19, 1999, may be appropriate for use in calculating the full term of the regulatory review period for this patent term extension application. Applicant will supplement this application with additional information concerning IND 57,939 and/or NDA 22-253 upon request by the Patent Office and/or the FDA.

11. A Brief Description Beginning On A New Page Of The Significant Activities Undertaken By The Marketing Applicant During The Applicable Regulatory Review Period With Respect To The Approved Product And The Significant Dates Applicable To Such Activities

A brief description of significant activities undertaken by the marketing applicant during the regulatory review period with respect to the approved product is annexed as **Exhibit F**. This exhibit provides a chronology of the major communications between the marketing applicant and the Food and Drug Administration, including a brief summary of the subject matter and date of these communications.

Applicant reserves the right to supplement the chronology of **Exhibit F** with materials from which it was derived or other evidence related to Applicant's conduct in obtaining the approval of VIMPAT® injection. *See, e.g.*, 21 CFR § 60.32.

12. A Statement Beginning On A New Page That In The Opinion Of The Applicant The Patent Is Eligible For The Extension And A Statement As To The Length Of The Extension Claimed, Including How The Length Of Extension Was Determined

Applicant is of the opinion that U.S. Patent No. Re38,551 is eligible for extension under 35 U.S.C. § 156, because it satisfies all of the requirements for such extension as follows:

a. 35 U.S.C. §156(a); 37 CFR §1.720(a)

U.S. Patent No. Re38,551 claims a product, and a method of using a product.

b. 35 U.S.C. §156(a)(1); 37 CFR §1.720(g)

The term of U.S. Patent No. Re38,551 has not expired before submission of this application.

c. 35 U.S.C. §156(a)(2); 37 CFR §1.720(b)

The term of U.S. Patent No. Re38,551 has never previously been extended under 35 U.S.C. §156.

d. 35 U.S.C. §156(a)(3); 37 CFR §1.730

This application for extension is submitted by the authorized agent or the owner of record in accordance with the requirement of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office.

e. 35 U.S.C. §156(a)(4); 37 CFR §1.720(d)

The product VIMPAT® injection has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use.

f. 35 U.S.C. §156(a)(5)(A); 37 CFR §1.720(e)(i)

The commercial marketing or use of the product VIMPAT® injection after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug, and Cosmetics Act (21 U.S.C. §360) under which such regulatory review period occurred.

g. 35 U.S.C. §156(c)(4); 37 CFR §1.720(h)

No other patent has been extended for the same regulatory review period for the product VIMPAT® injection.

h. 35 U.S.C. §156(d)(1); 37 CFR §1.720(f)

This application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use.

Applicant is of the opinion that U.S. Patent No. Re38,551 is eligible for extension under 35 U.S.C. § 156 for 1104 days as determined pursuant to 37 CFR §1.775 as follows:

Patent Information:

Patent 5,773,475 Issue Date	June 30, 1998
Earliest non-provisional priority date	March 17, 1997
Days Extension under 35 U.S.C. 154(b)	0

FDA Information:

Date IND Became Effective	November 14, 2003
Date NDA Submitted to the FDA	September 28, 2007
Date NDA Approved by the FDA	October 28, 2008

IND Period:	
Start Date of Regulatory Review Period	November 14, 2003
IND Period (days)	1414
½ IND Period (days)	707

Regulatory Review Period Allowed:	
NDA Review Period (days)	397
Regulatory Review Period (days)	1811
Reg. Rev. Period less ½ IND period (days)	1104

Statutory Limitations:	
Patent Expiration Date (20 year term)	March 17, 2017
Expiration under 5 year extension limitation (Date 1)	March 17, 2022
Expiration under 14 from NDA approval limitation (Date 2)	October 28, 2022
Expiration based upon full review period (Date 3)	March 25, 2020
Final Expiration Date (Earliest of Date 1, Date 2, or Date 3)	March 25, 2020
Maximum Extension in Days:	**1104**[2]

[2] All calculations above are performed assuming that November 14, 2003 is the appropriate date for when the relevant regulatory review period started. As noted above in footnote 1 on page 7, it is possible that the FDA could determine that a date as early as May 19, 1999 is the appropriate date for the start of the regulatory review period. Should that earlier date, or another earlier date, in fact be the appropriate start date for the regulatory review period, then Applicant would be entitled to a longer calculated review period, and thus a later "Date 3" above. For example, should the applicable regulatory review period be determined to have started on May 19, 1999, then the IND period will have lasted 3054 days, and the full regulatory review period will have lasted 3451 days. Thus, the regulatory review period less ½ IND period as calculated would be 1924 days. This would make the expiration of patent no. Re38,551 based upon the full regulatory review period (Date 3) be June 23, 2022. In this scenario, Applicant would be entitled to a full five-year extension of patent no. Re38,551, making it expire March 17, 2022 (i.e, Date 1 above).

13. A Statement That Applicant Acknowledges A Duty To Disclose To The Commissioner Of Patents And Trademarks And The Secretary Of Health And Human Services Any Information Which Is Material To The Determination Of Entitlement To The Extension Sought

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations of entitlement to the extension sought in the Application.

14. The Prescribed Fee For Receiving And Acting Upon The Application For Extension

The prescribed fee pursuant to 37 CFR §1.20(j) for receiving and acting upon this application is to be charged to the Deposit Account of Applicant's undersigned attorney as authorized in the attached letter.

15. The Name, Address, And Telephone Number Of The Person To Whom Inquiries And Correspondence Relating To The Application For Patent Term Extension Are To Be Directed

Please address all correspondence to:

Kevin G. Shaw
Hogan & Hartson, LLP
555 Thirteenth St., NW
Washington, DC 20004

16. A Duplicate Of The Application Papers, Certified As Such

Applicant hereby certifies that this application for extension is being filed in triplicate.

17. An Oath Or Declaration

Applicant, through its undersigned patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the agent or owner to act on behalf of the agent or owner in patent matters, being duly warned that willful false statements are punishable by fine or imprisonment or both under section 1001 of Title 18, United States

Code and that willful false statements and the like may jeopardize the validity of this application and the patent to which it relates, states and declares that the following statements made based on his own knowledge are true and that all statements made on information and belief are believed to be true:

(1) The undersigned is registered to practice before the Patent and Trademark Office and is making this declaration as a patent attorney who has general authority to act on behalf of the applicant in patent matters.

(2) The undersigned has reviewed and understands the contents of the application being submitted pursuant to this section;

(3) The undersigned believes the patent is subject to an extension pursuant to 37 C.F.R. § 1.710 in the event of NDA approval and, in the interim, is subject to an extension pursuant to 37 C.F.R. § 1.790;

(4) The undersigned believes an extension of the length claimed is justified under 35 U.S.C. 156 and the applicable regulations; and

(5) The undersigned believes the patent for which extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720 in the event of NDA approval, and meets the requirements for an interim extension of a patent set forth in 37 C.F.R. § 1.790.

If this application for extension of patent term is held to be informal, applicant may seek to have that holding reviewed by filing a petition with the required fee, as necessary, pursuant to 37 C.F.R. §§ 1.181, 1.182 or 1.183, as appropriate, within such time as may be set in any notice that the application has been held to be informal, or if no time is set, within one month of the date on which the application was held informal.

Respectfully submitted,

Dated: December 23, 2008

By: _____
Kevin G. Shaw
Registration No. 43,110

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555 13th Street, N.W.
Washington, D.C. 20004
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Exhibit A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re:	U.S. Patent No. RE38,551
Inventor:	KOHN, Harold
Original Issue Date:	June 30, 1998
Reissue Issue Date:	July 6, 2004
For:	ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES
Assignee:	Research Corporation Technologies, Inc.
Attorney Docket:	32555-0002-3

POWER OF ATTORNEY FOR PATENT TERM EXTENSION APPLICATION

Research Corporation Technologies, Inc., a non-profit corporation organized and existing under the laws of Delaware, and having a principal place of business at 5210 E. Williams Circle, Suite 240, Tucson, Arizona 85711-4410, represents that it is the owner of the entire interest in and to U.S. Patent No. Re38,551, granted to Harold Kohn for "Anticonvulsant Enantiomeric Amino Acid Derivatives," as reflected in the assignment document recorded by the U.S. Patent and Trademark Office on May 22, 1997 at Reel 008538, Frame 0093.

Research Corporation Technologies, Inc. hereby revokes all previous powers of attorney and appoints Kevin G. Shaw and the registered practitioners of Hogan & Hartson, L.L.P. included in the Customer Number provided below to prosecute this patent term extension application and to transact all business in the Patent and Trademark Office connected therewith, and further directs that all correspondence be addressed to Kevin G. Shaw at that Customer Number. The undersigned, acting in the official capacity stated below, has authority to and does hereby execute this document on behalf of Research Corporation Technologies, Inc.

Customer Number: 24633

Please direct all inquiries to:

Kevin G. Shaw
Telephone: (202) 637-6466
Facsimile: (202) 637-5910

Shaun A. Kirkpatrick
President & CEO
Research Corporation Technologies, Inc.
5210 E. Williams Circle, Suite 240
Tucson, AZ
85711-4410

December 19, 2008
Date

Exhibit B

SCHWARZ
PHARMA
A member of the UCB Group, Inc.

LETTER OF RELIANCE

Mail Stop Hatch-Waxman PTE
Office of Patent Legal Administration
Room MDW 7D55
600 Dulany Street (Madison Building)
Alexandria, VA 22314

Attn: Mary C. Till, Examiner
Office of Patent Legal Administration

Schwarz Biosciences, Inc. (having its registered office at 1209, Orange Street, Wilmington, Delaware 19801, USA; "SBI") is directly held by UCB Inc. (having its registered office at 1209, Orange Street, Wilmington, Delaware 19801, USA), the latter being a directly and indirectly wholly-owned subsidiary of UCB Holdings, Inc. (having its registered office at 1209, Orange Street, Wilmington, Delaware 19801, USA) which is directly wholly-owned subsidiary of UCB S.A. (having its registered office at Allée de la Recherche 60, 1070 Brussels, Belgium).

Schwarz Pharma AG (having its registered office at Alfred-Nobel Strasse 10, 40789 Monheim, Germany; "SPAG") is directly held by UCB SP GmbH (having an office at Alfred-Nobel Strasse 10, 40789 Monheim, Germany) which is a directly wholly-owned subsidiary of UCB GmbH (having its registered office at Alfred-Nobel Strasse 10, 40789 Monheim, Germany), the latter being directly and indirectly held by UCB S.A. (having its registered office at Allée de la Recherche 60, 1070 Brussels, Belgium).

SPAG has exclusive license rights regarding lacosamide, R-2-Acetamido-N-benzyl-3-methoxypropionamide, under U.S. Patent Nos. Re38,551 and 5,654,301, as sublicensee of Harris FRC Corporation (having an office at 2137 Route 35 Holmdel, New Jersey 07733; "Harris FRC") that is licensee from Research Corporation Technologies, Inc. (having an office at 5210 E. Williams Circle, Suite 240, Tucson, Arizona 85711-4410; "RCT"). Hence, SPAG, Harris FRC, and RCT are sublicensee, licensee and assignee, respectively, of U.S. Patent Nos. Re38,551 and 5,654,301.

SBI, as NDA holder, authorizes RCT to rely on activities of SBI and its predecessors in interest relating to FDA approval of VIMPAT® lacosamide products as adjunctive therapy in treatment of partial-onset seizures in patients with epilepsy, in Tablet form under NDA 22-253 and in Injection form under NDA 22-254, in support of RCT's intension to apply for extension of patent term of U.S. Patent Nos. Re38,551 and 5,654,301,as provided under 35 U.S.C. §156(d) (1), 37 C.F.R. §1.730 and MPEP 2752.

SCHWARZ
PHARMA

Authorized by Schwarz Biosciences, Inc.

By: Patricia A Hartz for Deborah Hogerman Date: 12-01-08

Deborah Hogerman
Senior Director, U.S. Regulatory Affairs
On behalf of Schwarz Biosciences, Inc.

cc: Research Corporation Technologies, Inc.
cc: Harris FRC Corporation

Exhibit C

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA APPROVAL

NDA 22-253
NDA 22-254

Schwarz Biosciences, Inc.
Attention: Alan Blumberg
Senior Director, US Regulatory Affairs
P.O. Box 110167
Research Triangle Park, NC 27709

Dear Mr. Blumberg:

Please refer to your new drug applications (NDAs) dated September 28, 2007, received September 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Vimpat (lacosamide) Tablets, 50 mg, 100 mg, 150 mg, and 200 mg, and Vimpat (lacosamide) Injection, 200 mg per 20 ml.

We acknowledge receipt of your additional submissions dated:

November 26, 2007	March 20, 2008	April 30, 2008	July 17, 2008	September 4, 2008
December 13, 2007	April 3, 2008	May 9, 2008	July 30, 2008	September 23, 2008
January 23, 2008	April 9, 2008	May 27, 2008	August 1, 2008	October 15, 2008
February 13, 2008	April 14, 2008	June 11, 2008	August 14, 2008	October 21, 2008
February 22, 2008	April 18, 2008	July 11, 2008 (2)	August 27, 2008	

These new drug applications provide for the use of Vimpat (lacosamide) as follows:

- Vimpat (lacosamide) Tablets as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.

- Vimpat (lacosamide) Injection as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible.

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Your applications for Vimpat (lacosamide) Tablets and Injection (NDA 22-253, 22-254) were not referred to an FDA advisory committee because your products are members of the class of previously approved anti-epileptic drugs and the products did not pose unique concerns beyond those applicable to other members of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 1 month for these applications because necessary studies are impossible or highly impracticable because there are too few children with partial onset seizures in this age group to study.

In addition, we are deferring submission of your pediatric studies in partial onset seizures for ages 1 month up to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

1. Deferred pediatric studies under PREA for the adjunctive treatment of partial onset seizures in pediatric patients ages 1 month up to 17 years.

   Final Report Submission: July 2013

Submit final study reports to these NDAs. For administrative purposes, all submissions related to these required pediatric postmarketing studies must be clearly designated "**Required Pediatric Assessment.**"

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Title IX, Subtitle A, Section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Vimpat (lacosamide) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is

necessary for patients' safe and effective use of Vimpat (lacosamide). FDA has determined that Vimpat (lacosamide) has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Vimpat (lacosamide). In addition, patient labeling could help prevent serious adverse effects related to the use of these products. Vimpat (lacosamide) may increase the risk of suicidal thoughts or behavior in patients taking anti-epileptic drugs for any indication. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Vimpat (lacosamide).

Your proposed REMS, submitted on October 17, 2008, in an electronic communication, is approved. The REMS consists of the Medication Guide included with this letter and the timetable for submission of assessments of the REMS included in your October 17, 2008 submission.

Prominently identify submissions containing REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission:

- **NDA 22-253 & 22-254 REMS ASSESSMENT**
- **NEW SUPPLEMENT FOR NDA 22-253 & 22-254**
  PROPOSED REMS MODIFICATION
  < other supplement identification > [if included]
  <REMS ASSESSMENT> [if included]

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of FDAAA amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A)).

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of developmental neurotoxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) has not yet been established and is not sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following study:

2. A nonclinical study in rats to examine the effects of Vimpat (lacosamide) on brain development during the prenatal and early postnatal periods using more sensitive techniques for assessing central nervous system structure and function than were employed in the standard pre- and postnatal development study. You should consider the use of multiple daily dosing as a means of achieving higher plasma drug exposures during pregnancy and to better mimic the human exposure pattern.

The timetable you have submitted on October 28, 2008 states that you will conduct this study according to the following schedule:

Protocol Submission:	Within 6 months of approval
Final Report Submission:	Within 30 months of approval

Submit protocols to your IND 57,939 with a cross-reference letter to these new drug applications (NDA) 22-253 and 22-254. Submit final reports to your NDAs 22-253 and 22-254. Please use the following designators to label prominently all submissions, including supplements, relating to this postmarketing study as appropriate:

- **Required Postmarketing Protocol under 505(o)**
- **Required Postmarketing Final Report under 505(o)**
- **Required Postmarketing Correspondence under 505(o)**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS

We acknowledge your written commitment to conduct the following postmarketing study as described in your submission dated October 28, 2008, as outlined below:

3. *In vitro* data to determine which enzymes may be involved in the metabolism of Vimpat (lacosamide) in addition to CYP2C19.

Final Report Submission:	within 18 months of approval

Submit the protocol to your IND (b)(4). Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to these NDAs. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to these NDAs. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study.

All submissions, including supplements, relating to these postmarketing study commitments should be prominently labeled:

- **Postmarketing Study Commitment Protocol**
- **Postmarketing Study Commitment Final Report**
- **Postmarketing Study Commitment Correspondence**

HIGHLIGHTS WAIVER

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling (text for the package insert and Medication Guide). Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, **"SPL for approved NDA 22-253 and NDA 22-254."**

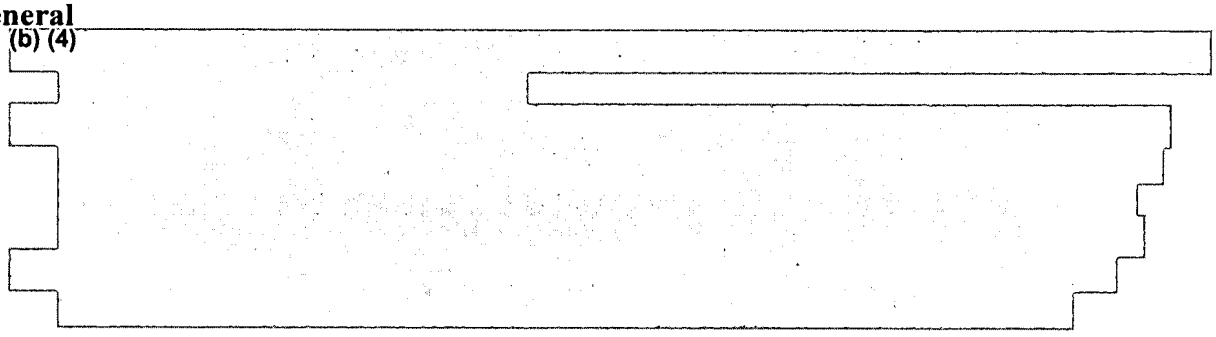
CARTON AND IMMEDIATE CONTAINER LABELS

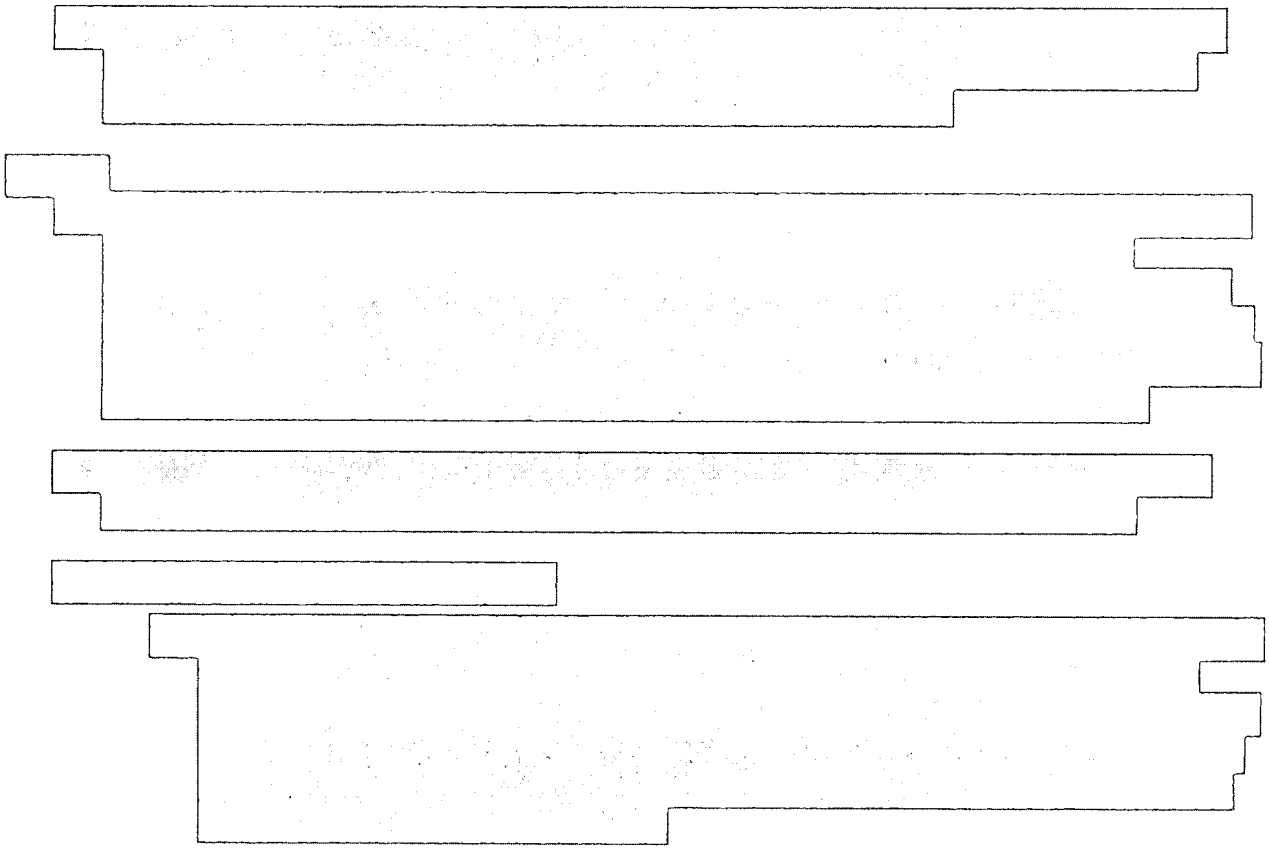
Submit final printed carton and container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 22-253 and NDA 22-254**" Approval of this submission by FDA is not required before the labeling is used.

In addition, we note your agreement on October 28, 2008 to address and make the following changes into your carton and immediate container labels:

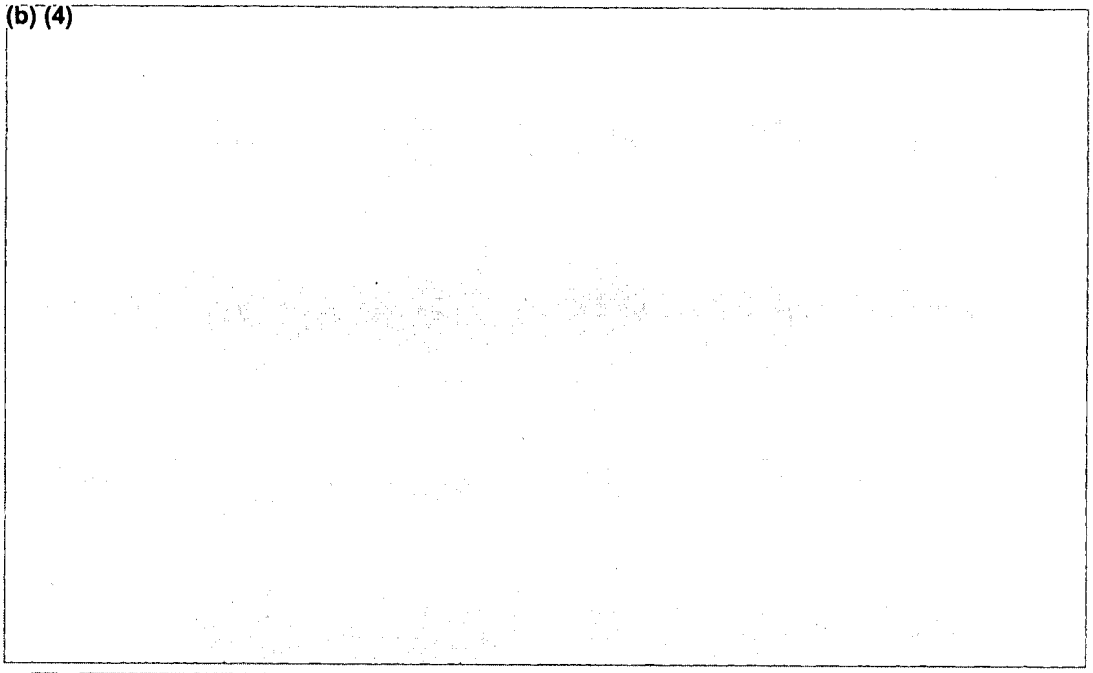
General

(b) (4)

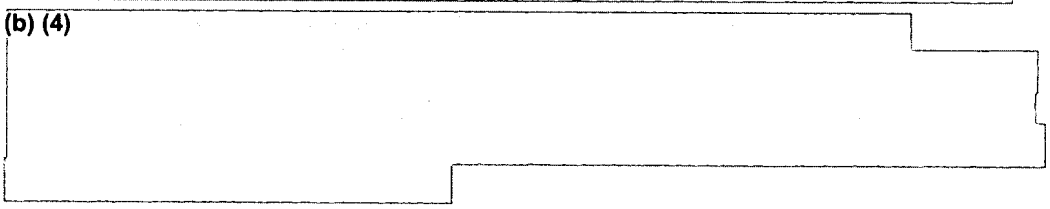




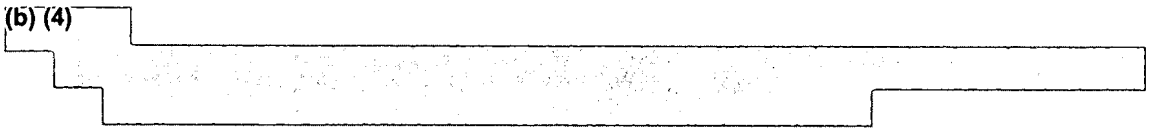
(b) (4)



(b) (4)



(b) (4)



Marketing the products with FPL that is not identical to the approved labeling text including the changes noted above may render the product misbranded and an unapproved new drug.

CONTROLLED SUBSTANCE CLASS

We have recommended that this product be scheduled under the Controlled Substances Act. We remind you of the following statement that appears on the Form FDA 356h, "If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision." Once a final scheduling decision is made, your label must be amended to reflect the schedule.

EXPIRATION DATE (Injection)

We grant the proposed 36 month drug product expiry, when stored at controlled room temperature, for lacosamide 200 mg/20 mL injection packaged in 20 mL type I colorless glass vials with a grey rubber stopper coated with a (b) (4) and aluminum overseal.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

LETTERS TO HEALTH CARE PROFESSIONALS

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Jacqueline H. Ware, Pharm.D., Supervisory Regulatory Project Manager, at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Deputy Director (Acting)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures (FDA Approved Labeling Text, Medication Guide, and REMS document)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Ellis Unger
10/28/2008 08:00:13 PM

Exhibit D

US00RE38551E1

(19) **United States**

(12) **Reissued Patent**
Kohn

(10) **Patent Number: US RE38,551 E**

(45) **Date of Reissued Patent: Jul. 6, 2004**

(54) **ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES**

(75) Inventor: **Harold Kohn**, Chapel Hill, NC (US)

(73) Assignee: **Research Corporation Technologies, Inc.**, Tucson, AZ (US)

(21) Appl. No.: **10/058,634**

(22) Filed: **Jan. 28, 2002**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,773,475**
Issued: **Jun. 30, 1998**
Appl. No.: **08/818,688**
Filed: **Mar. 17, 1997**

U.S. Applications:

(60) Provisional application No. 60/013,522, filed on Mar. 15, 1996.

(51) **Int. Cl.**[7] **A61K 31/165**; C07C 233/05

(52) **U.S. Cl.** **514/616**; 564/155; 564/158

(58) **Field of Search** 514/616; 564/155, 564/158

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,378,729	A	1/1995	Kohn et al.	514/231.2
5,654,301	A	8/1997	Kohn et al.	514/231.2

FOREIGN PATENT DOCUMENTS

EP	0 194 464	9/1986	

OTHER PUBLICATIONS

Anderson, et al. *J. Am. Chem. Soc.* 89:19 pp. 5012–5017, (1967).

Kohn, Harold, et al. "Preparation and anticonvulsant activity of a series of functionalized. alph.–heteroatom–substituted amino acids", *J. Med. Chem.* 34, 2444–2452 (1991).

Kohn, Harold, et al. "Marked stereospecificity in a new class of anticonvulsants", *Chemical Abstracts,* 109 (1988) Abstract No. 183045.

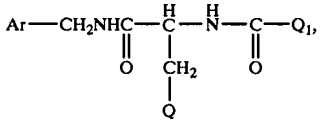
Choi, Daeock, et al. "Synthesis and Anticonvulsant Activities of N–Benzyl–2–acetamidopropionamide Derivatives", *J. Med. Chem.,* 39: 1907–1916 (1996).

Primary Examiner—Shailendra Kumar

(74) *Attorney, Agent, or Firm*—Scully, Scott, Murphy & Presser

(57) **ABSTRACT**

The present invention is directed to a compound in the R configuration about the asymmetric carbon in the following formula:



pharmaceutical compositions containing same and the use thereof in treating CNS disorders in animals.

13 Claims, No Drawings

ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

RELATED APPLICATION

This application claims priority from U.S. provisional application No. 60/013,522 filed on Mar. 15, 1996.

GOVERNMENT SUPPORT

This invention was made with Government support under Grant/Contract No. NIH MS 15604 awarded by the National Institute of Health. The Government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention relates to novel enantiomeric compounds and pharmaceutical compositions useful in the treatment of epilepsy and other CNS disorders.

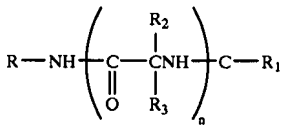
BACKGROUND OF THE INVENTION

The predominant application of anticonvulsant drugs is the control and prevention of seizures associated with epilepsy or related central nervous system disorders. Epilepsy refers to many types of recurrent seizures produced by paroxysmal excessive neuronal discharges in the brain; the two main generalized seizures are petit mal, which is associated with myoclonic jerks, akinetic seizures, transient loss of consciousness, but without convulsion; and grand mal which manifests in a continuous series of seizures and convulsions with loss of consciousness.

The mainstay of treatment for such disorders has been the long-term and consistent administration of anticonvulsant drugs. Most drugs in use are weak acids that, presumably, exert their action on neurons, glial cells or both of the central nervous system. The majority of these compounds are characterized by the presence of at least one amide unit and one or more benzene rings that are present as a phenyl group or part of a cyclic system.

Much attention has been focused upon the development of anticonvulsant drugs and today many such drugs are well known. For example, the hydantions, such as phenytoin, are useful in the control of generalized seizures and all forms of partial seizures. The oxazolidinediones, such as trimethadione and paramethadione, are used in the treatment of nonconvulsive seizures. Phenacemide, a phenylacetylurea, is one of the most well known anticonvulsants employed today, while much attention has recently been dedicated to the investigation of the diazepines and piperazines. For example, U.S. Pat. Nos. 4,002,764 and 4,178,378 to Allgeier, et al. disclose esterified diazepine derivatives useful in the treatment of epilepsy and other nervous disorders. U.S. Pat. No. 3,887,543 to Nakanishi, et al. describes a thieno [2,3-e][1,4]diazepine compound also having anticonvulsant activity and other depressant activity. U.S. Pat. No. 4,209,516 to Heckendorn, et al. relates to triazole derivatives which exhibit anticonvulsant activity and are useful in the treatment of epilepsy and conditions of tension and agitation. U.S. Pat. No. 4,372,974 to Fish, et al. discloses a pharmaceutical formulation containing an aliphatic amino acid compound in which the carboxylic acid and primary amine are separated by three or four units. Administration of these compounds in an acid pH range are useful in the treatment of convulsion disorders and also possess anxiolytic and sedative properties.

U.S. Pat. No. 5,378,729 to Kohn, et al. discloses compounds and pharmaceutical compositions having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders having the following general formula:



R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cyclòalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group, or electron donating group.

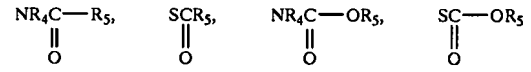
R_1 is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group and

R_2 and R_3 are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z—Y wherein R_2 and R_3 may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, S, S $(O)_a$, NR_4, PR_4 or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic, or heterocyclic lower alkyl, and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond, or

ZY taken together is $NR_4NR_5R_7$, NR_4OR_5, ONR_4R_7, OPR_4R_5, PR_4OR_5, SNR_4R_7, NR_4SR_7, SPR_4R_5, PR_4SR_7, $NR_4PR_5R_6$, $PR_4NR_5R_7$,



R_4, R_5 and R_6 are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R_4, R_5 and R_6 may be unsubstituted or substituted with an electron withdrawing group or an electron donating group,

R_7 is R_6, $COOR_8$ or COR_8,

R_8 is hydrogen, lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

n is 1–4 and

a is 1–3.

Unfortunately, despite the many available pharmacotherapeutic agents, a significant percentage of the population with epilepsy or related disorders are poorly managed. Moreover, none of the drugs presently available are capable of achieving total seizure control, and most have disturbing side effects. Toxicities may appear upon repeated dosing that are

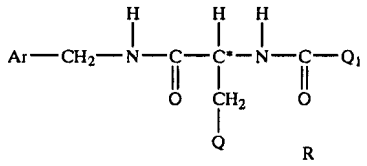
not apparent with acute administration. Because many drugs which require chronic administration ultimately place an extra burden on the liver, including for example, liver enzyme induction or oxidative metabolism that may generate reactive species, many anticonvulsants have associated therewith liver toxicity.

Research is continuing in this area to find better and more effective anticonvulsant agents, especially for long term treatment (chronic administration). Obviously, the ideal drug is one that has high pharmacological activity, minimal side effects and is relatively non-toxic and safe to the animal that is being treated. More specifically, the ideal anticonvulsant drug is one that satisfies the following four criteria: (1) has a high anticonvulsant activity, (expressed as a low ED_{50}); (2) has minimal neurological toxicity, (as expressed by the median toxic dose (TD_{50})), relative to its potency; (3) has a maximum protective index (sometimes known as selectivity or margin of safety), which measures the relationship between the doses of a drug required to produce undesired and desired effects, and is measured as the ratio between the median toxic dose and the median effective dose (TD_{50}/ED_{50}); and (4) is relatively safe as measured by the median lethal dose (LD_{50}) relative to its potency and is non-toxic to the animal that is being treated, e.g., it exhibits minimal adverse effects on the remainder of the treated animal, its organs, blood, its bodily functions, etc. even at high concentrations, especially during long term chronic administration of the drug. Thus, for example, it exhibits minimal, i.e., little or no liver toxicity. Although not as critical in short term or acute administration of an anticonvulsant, since the animal may tolerate some low levels of toxicity, the fourth criteria outlined above is extremely important for an anti-convulsant which is to be taken over a long period of time (chronic administration) or in high dosage. It may be the most important factor in determining which anti-convulsant to administer to a patient, especially if chronic dosing is required. Thus, an anti-convulsant agent which has a high anti-convulsant activity, has minimal neurological toxicity and maximal P.I. (protective index) may unfortunately exhibit such toxicities which appear upon repeated high levels of administration. In such an event, acute dosing of the drug may be considered, but it would not be used in a treatment regime which requires chronic administration of the anti-convulsant. In fact, if an anti-convulsant is required for repeated dosing in a long term treatment regime, a physician may prescribe an anti-convulsant that may have weaker activity relative to a second anti-convulsant, if it exhibits relatively low toxicity to the animal. An anti-convulsant agent which meets all four criteria is very rare.

However, the present inventor has found such a group of compounds that is generally potent, exhibit minimal neurological toxicity, has a high protective index and is relatively non-toxic to the body organs, including the liver upon multiple dosing.

SUMMARY OF THE INVENTION

Accordingly, the present invention is directed to N-benzyl-2-acetamido propionamide derivatives in the R configuration having the formula:



I

wherein

Ar is aryl which is unsubstituted or substituted with halo;

Q is lower alkoxy; and

Q_1 is CH_3.

The present invention contemplates employing the compound of Formula I in a pharmaceutical composition. Moreover, the administration of an effective amount of the present compounds in their pharmaceutically acceptable forms provides an excellent regime for the treatment of epilepsy, nervous anxiety, psychosis, insomnia, and other related central nervous disorders.

These drugs exhibit high anti-convulsant activity, minimal neurological toxicity, high P.I. and minimal toxicity. These anti-convulsants are utilized in a treatment regime requiring acute dosing, and especially chronic dosing thereof to the patient.

As shown hereinbelow, the compounds of the present invention exhibit minimal effects on liver, which is in contrast to other anti-convulsant compounds.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the term "alkoxy" refers to an O-alkyl group attached to the main chain through an oxygen bridge, wherein alkyl is as defined hereinabove. The alkoxy groups are lower alkoxy groups containing one to six carbon atoms, and more preferably, one to three carbon atoms. The most preferred alkoxy groups are propoxy, isopropoxy, ethoxy and especially methoxy.

The term "aryl", when used alone or in combination, refers to a phenyl group which is unsubstituted or substituted with halo.

The term halo includes fluoro, chloro, bromo, iodo and the like. The preferred halo is fluoro.

It is preferred that Q in the compound of formula I is alkoxy having 1–3 carbon atoms. The most preferred alkoxy group is propoxy, isopropoxy, ethoxy and especially methoxy.

The Ar group as defined herein, is phenyl, which may be unsubstituted or substituted as defined herein. It is most preferred that the aryl group, i.e., phenyl, is unsubstituted or substituted with only one halo group. It is more preferred that if substituted, the halo substituent is in the para or meta position. It is even more preferred that the phenyl group is unsubstituted.

Examples of the compounds of the present invention include:

(R)-N-Benzyl-2-acetamido-3-methoxy propionamide,

(R)-N-(3-Fluorobenzyl)-2-acetamido-3-methoxypropionamide,

(R)-N-(4-Fluorobenzyl)-2-acetamide-3-methoxypropionamide,

(R)-N-Benzyl-2-acetamido-3-ethoxy propionamide.

As indicated by the asterisk in formula I, the compounds of the present invention contain at least one asymmetric carbon. The stereochemistry of the asymmetric carbon at the

asterisk is in the R configuration. The inventor has found that the R stereoisomer at the asymmetric carbon at the asterisk is significantly more efficacious than the corresponding S enantiomer or a racemic mixture thereof.

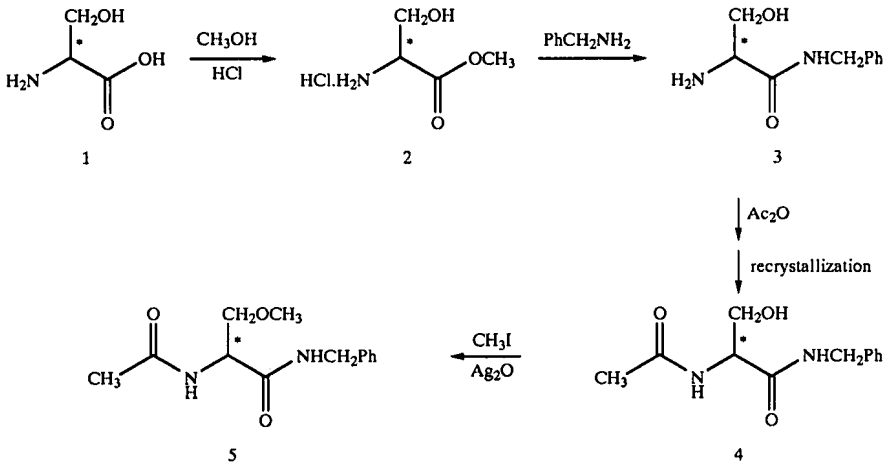
It is preferred that the compound of the present invention be substantially pure, i.e., substantially free from impurities. It is most preferred that the compounds of the present invention be at least 75% pure (w/w) and more preferably greater than about 90% pure (w/w) and most preferably greater than about 95% pure (w/w).

It is also preferred that the compounds of the present invention be substantially enantiomerically pure, i.e., substantially free from the corresponding S isomer. It is more preferred that the compounds of the present invention contain at least 90% (w/w) R stereoisomer, and most preferably greater than about 95% (w/w) in the R stereoisomer. Thus, the present invention contemplates compounds having at most about 10% S isomer (w/w), and even more preferably less than about 5% S isomer (w/w).

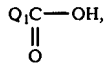
The compounds of the present invention in the R form are prepared by art recognized techniques from commercially available starting materials.

An exemplary procedure is outlined in Scheme 1 hereinbelow:

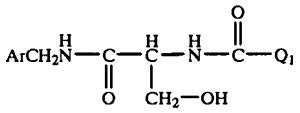
Scheme 1



A D serine molecule (1) is esterified under acylation conditions with an alcohol, such as acidic methanol, to provide the corresponding ester (2). 2 is reacted with $ArCH_2NH_2$, such as benzylamine, under acylation conditions to form the corresponding amide (3). Acylation of the free amino group, with an acylating derivative of



such as acetic acid, or lower alkyl ester of acetic acid, or acetic anhydride provides the hydroxymethyl derivative, i.e.,

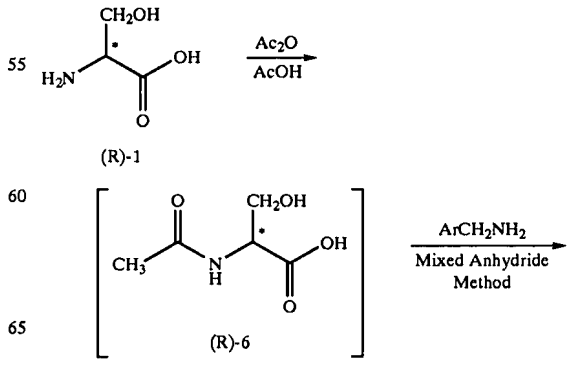


(4)

The enantiopurity of 4 was determined by techniques known in the art, including melting point, optical rotation and ^1H NMR upon addition of an organic acid in the R-configuration, such as R(−)- mandelic acid. Crystallization of 4 was repeated until the desired enantiopurity thereof was achieved. The product of 4 is converted to the ether under Williamson conditions by reacting it with QX, wherein Q is as defined herein above and X is good leaving groups, such as OTs, OMs, or halide (e.g., CH_3I) and the like in the presence of base (e.g., Ag_2O) to form the product (5) having Formula I.

Another variation is depicted in Scheme 2.

Scheme 2



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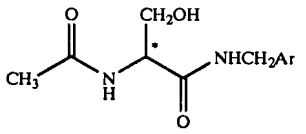
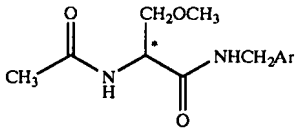
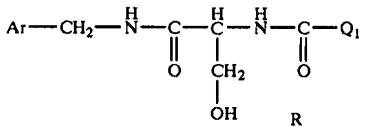


(R)-7



(R)-8

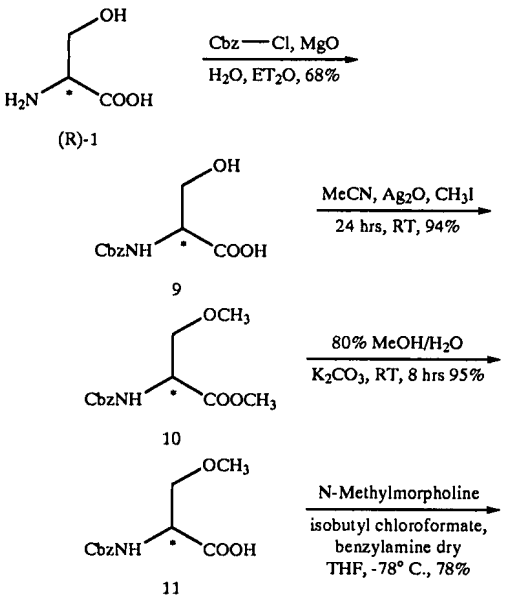
For example, beginning with D-serine (1), treatment with an acylating derivative of acetic acid such as acetic anhydride in acetic acid, gives the corresponding amide 6 which is then reacted with $ArCH_2NH_2$ under mixed anhydride coupling reaction conditions, as described by Anderson, et al., in JACS, 1967, 89, 5012–5017, the contents of which are incorporated herein by reference, to give the corresponding compound of the formula:



e.g., 7. Alkylation of this R-product in the presence of base under Williamson conditions, such as methyl iodide in Ag_2O, provides a product of Formula I (8).

An alternative route is depicted in Scheme 3.

Scheme 3



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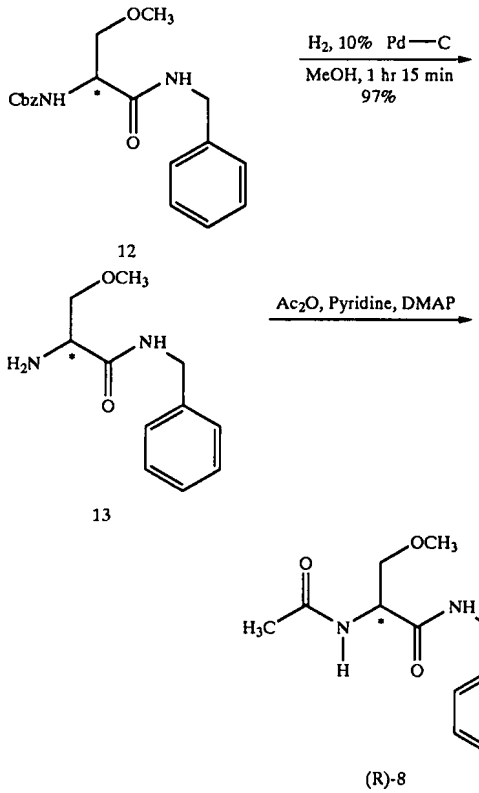

(R)-8

D Serine (1) is protected with a N-protecting group known in the art, by standard techniques. Thus, for example, it is reacted with carbobenzoxy chloride (CBZ-cl, benzyl chloroformate) generating the N-protected CBZ-D-serine adduct 9. The product serine adduct is converted to the corresponding ether under Williamson conditions by reacting it with QX wherein Q and X are defined hereinabove (e.g., CH_3I) in the presence of base (e.g., Ag_20) to form an ether 10. Under these conditions, the acid is also esterified. Subsequent hydrolysis of the ester group in 10 permits amide coupling with $ArCH_2$ NH_2 using amide coupling methodology (e.g., mixed anhydride 1,1' Carbonyldiimidazole) to give the amide 12. Deprotection of the N-protecting group provide the free amine 13 which is then reacted with an acylating agent such as acetic anhydride in base, (e.g., pyridine) to provide the product (R)-8.

If necessary, in any of the procedures described hereinabove, the optical purity of the product may be enhanced by further separation of the S enantiomer from the R enantiomer, by standard techniques known in the art, such as chiral chromatography using a standard chiral support known in the art.

Alternatively, in any of the procedures provided hereinabove, a racemic D serine may be utilized as the starting material. Following the procedures in any of the schemes outlined hereinabove would provide the racemic mixture, which can be resolved into the R isomer by standard techniques known in the art such as chiral chromatography.

The active ingredients of the therapeutic compositions and the compounds of the present invention exhibit excellent anticonvulsant activity when administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For

example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation. A decided practical advantage is that the active compound may be administered in an convenient manner such as by the oral, intravenous (where water soluble), intramuscular or subcutaneous routes.

The active compound may be orally administered, for example, with an inert diluent or with an assimilable edible carrier, or it may be enclosed in hard or soft shell gelatin capsules, or it may be compressed into tablets, or it may be incorporated directly into the food of the diet. For oral therapeutic administration, the active compound may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 5 to about 80% of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that a suitable dosage will be obtained. Preferred compositions or preparations according to the present invention are prepared so that an oral dosage unit form contains between about 5 and 100 mg of active compound.

The tablets, troches, pills, capsules and the like may also contain the following: A binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring. When the dosage unit form is a capsule, it may contain, in addition of materials of the above type, a liquid carrier. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and formulations. For example, sustained release dosage forms are contemplated wherein the active ingredient is bound to an ion exchange resin which, optionally, can be coated with a diffusion barrier coating to modify the release properties of the resin.

The active compound may also be administered parenterally or intraperitoneally. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredient into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from previously sterile-filtered solution thereof.

As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifics for the novel dosage unit forms of the invention are dictated by and directly, dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as herein disclosed in detail.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore described. A unit dosage form can, for example, contain the principal active compound in amounts ranging from about 5 to about 1000 mg. Expressed in proportions, the active compound is generally present in from about 1 to about 750 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

Unless indicated to the contrary, percentages are by weight.

As used herein, the term lower alkyl refers to an alkyl group containing 1–6 carbon atoms which may be straight chained or branched.

For a better understanding of the present invention reference is made to the following description and examples.

GENERAL METHODS

Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on Perkin-Elmer 1330, 283 and a Mattson Genesis spectrometer and were calibrated against the 1601 cm^{-1} bond of polystyrene. Absorption values are expressed in wave-numbers (cm^{-1}). Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were taken on Nicolet NT-300 and General Electric QE-300 NMR instruments. Chemical shifts (δ) are in parts per million (ppm) relative to Me_4Si and coupling constants (J values) are in hertz. All chemical ionization mass spectral investigations were conducted on Finnegan MAT TSQ-70 instrument. Microanalyses were provided by Atlantic Microlab Inc. (Norcross, Ga). Thin layer chromatography was performed on precoated silica gel GHLF microscope slides (2.5x10 cm; Analtech No. 21521).

EXAMPLE 1

(R)-N-Benzyl-2-Acetamide-3-methoxypropionamide

Hydrochloric acid (8.00 g, 219.4 mmol) was passed into MeOH (250 mL) and then D-Serine (20.00 g, 190.3 mmol) was added. The reaction solution was heated at reflux (18 hours), benzylamine (81.6 mL, 761 mmol) was added and then the reaction was heated for an additional eighteen hours. The solvent was removed under reduced pressure, the insoluble salts filtered, and the excess benzylamine was removed under high vacuum (Kugelrohr). The residue was dissolved in water (100 mL), and the product was extracted with $CHCl_3$ (8x200 mL). The organic layers were combined, dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was triturated with Et_2O (150 mL) and filtered to give 10.0 g (27%) of the product R-enriched N-benzyl 2-aminohydracrylamide, as a white solid: mp 74°–78° C.; $[\alpha]_D^{23}$ (c=1, MeOH)=1.6°, R_f 0.30 (10% MeOH—$CHCl_3$); ^1H NMR (DMSO-d_6) δ1.87 (br s, NH_2), 3.23 (t, J=5.4 Hz, CH), 3.39–3.55 (m, CH_2OH), 4.28 (d, J=5.7 Hz, $NHCH_2$) 4.76 (t, J=5.4 Hz, CH_2OH), 7.18–7.32 (m, 5PhH), 8.34 (t, J=5.7 Hz, NH), ^{13}C NMR (DMSO-d_6) 41.8 ($NHCH_2$), 56.9 (CH), 64.3 (CH_2OH), 126.6 (C_4'), 127.0 ($2C_2'$ or $2C_3'$), 128.1 ($2C_2'$ or 2C3'), 139.5 C_1'), 173.3 (C(O)NH) ppm, MS (+Cl) (rel intensity), 195 (M^++1, 53), 117 (100), Mr(+Cl) 195.113 56 (M^++1) (calcd. for $C_{10}H_{15}N_2O_2$, 195.11335).

To a stirred methylene chloride suspension (100 ml) of R enriched N-benzyl-2-aminohydracrylamide (10.00 g, 51.5 mmol) was added acetic anhydride (5.8 mL, 61.8 mmol), and the reaction suspension was stirred at room temperature (1 hour). The solvent was removed under reduced pressure to give a white solid. The product was triturated with Et_2O (250 mL) to give 7.60 g (62%) of enriched R-N-benzyl-2-acetamidohydracrylamide as a white solid. The reaction product was recrystallized (2x) using EtOH to give 3.50 g (29%) of the R-N-benzyl-2-acetamidohydracylamide mp 148°–149° C.; $[\alpha]_D^{23}$ (c=1, MeOH)=+22.4°; Rf 0.40 (10% MeOH—$CHCl_3$); IR (KBr) 3295, 3090, 2964, 1642, 1533, 1376, 1281, 1051, 705 cm; ^1H NMR (DMSO-d_6) δ1.86 (s, $C(O)CH_3$), 3.57 (dd, J=5.7, 5.7 Hz, CH_2OH), 4.25–4.31(m, CH), 4.27 (d, J=5.7 Hz, $NHCH_2$), 4.92 (t, J=5.7 Hz, CH_2OH), 7.18–7.32 (m, 5 PhH) 7.94 (d, J=7.8Hz, NH), 8.38 (t, J=5.7 H, NH), addition of excess R-(–) mandelic acid to a $CDCl_3$ solution of R-N-benzyl 2-acetamidohydracrylamide prepared hereinabove gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 ($C(O)CH_3$), 42.0 (CH_2NH), 55.6 (CH), 61.8(CH_2OH), 126.7 (C_4'), 127.0 ($2C_2'$ or $2C_3'$), 128.2 ($2C_2'$ or $2C_3'$), 139.4 (C_1'), 169.5 ($C(O)CH_3$ or C(O)NH), 170.3 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) rel intensity) 237 (M^++1, 100), 219(8); Mr(+Cl) 237.12388 [M^++1] (calcd for $C_{12}H_{17}N_2O_3$ 237.12392); Anal ($C_{12}H_{16}N_2O_3$), C,H,N.

To a stirred acetonitrile solution (300 mL) of (R)-N-benzyl-2-acetamidohydroacrylamide (2.36 g, 10 mmol) was successively added Ag_2O (11.59 g, 50 mmol) and methyl iodide (6.2 mL, 100 mmol) at room temperature. The reaction mixture was stirred at room temperature for 4 days. The insoluble salts were filtered, and the solvents were removed in vacuo to give a white solid. The residue was filtered with Et_2O (100 mL) to give 2.20 g (88%) of the above-identified product.

mp 143°–144° C.; $[\alpha]_D^{23}$ (c=1, MeOH)=+16.4°; Rf0.47 (10% MeOH—$CHCl_3$); IR (KBr) 3289, 3086, 2923, 2876, 2819, 1636, 1547, 1138, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.04 (s, $C(O)CH_3$), 3.38 (s, OCH_3), 3.43 (dd, J=7.8, 9.0 Hz, $CHH'OCH_3$), 3.82 (dd, J=4.2, 9.0 Hz, $CHH'OCH_3$), 4.48(d, J=6.0 Hz, $NHCH_2$), 4.51–4.57 (m,CH), 6.44 (br d, J=5.4 Hz, NH), 6.75 (br s, NH), 7.25–7.37 (m, 5 PhH), addition of excess (R)-(–)-mandelic acid to a $CDCl_3$ solution of (R)-18 gave only one signal for the acetyl methyl and ether methyl protons; ^{13}C NMR ($CDCl_3$) 23.2 ($C(O)CH_3$), 43.5 (CH_2NH), 52.4 (CH), 59.1 (OCH_3), 71.7 (CH_2OCH_3), 127.4 (C_4'), 127.5 ($2C_2'$ or $2C_3'$), 128.7 (2C2' or $2C_3'$), 137.9 (C_1'), 169.9 ($C(O)CH_3$ or C(O)NH), 170.3 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (rel intensity) 251 (M^++1, 100), 219(6); Mr (+Cl)251.139 76 [M^++1] (calcd for $C_{13}H_{19}N_2O_3$ 251.139 57); Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

EXAMPLE 2

Another Synthesis of (R)-N-Benzyl 2-Acetamide-3-methoxy propionamide

(a) Improved Synthesis of (R)-N-Benzyl 2-Acetamidohydracrylamide

To a stirred AcOH (20 mL) suspension of D-serine (5.26 g, 50 mmol) was added Ac_2O (4.7 mL, 50 mmol), and then the reaction suspension was stirred at room temperature (24 hours). The ACOH was removed in vacuo to give an oily residue, and then THF (150 mL) was added to the residue. The THF suspension was cooled to –78° C. under N_2 and 4-methylmorpholine (11.0 mL, 100 mmol) was added. After stirring for two minutes, isobutyl chloroformate (13.0 mL, 100 mmol) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for two additional minutes and then benzylamine (10.4 mL, 100 mmol) was added at –78° C. The reaction mixture was allowed to stir at room temperature (30 minutes) and the 4-methylmorpholine hydrochloride salt was filtered. The organic layer was concentrated in vacuo. The product was purified by flash column chromatography on SiO_2 gel (10% MeOH—$CHCl_3$) to give 3.89 g (33%) as a white solid mp 147°–148° C.; $[\alpha]_D^{23}$ (C=1, MeOH)=+21.70; ^1H NMR (DMSO-d_6) δ1.86 (s, C(O) CH_3), 3.57 (dd, J=5.1, 5.1 Hz, CH_2O), 4.27–4.31 (m, CH_2NH, CH), 4.90 (t, J=5.1 Hz, OH), 7.20–7.31 (m, 5 PhH), 7.93, (d, J=8.1 Hz, NH), 8.37 (t, J=6.0 Hz, NH), addition of excess (R)-(–)-mandelic acid to a $CDCl_3$ solution of the product of (a) gave only one signal for the acetyl methyl protons.

(b) (R)-N-Benzyl-2-Acetamide-3-methoxypropionamide

To the compound prepared in (a) (1.42 g, 6 mmol) in a stirred solution (300 ml) of CH_3CN was successively added

Ag_2O (6.95 g, 30 mmol) and methyl iodide (3.7 mL, 60 mmol) and stirred at room temperature for 4 days. The insoluble salts were filtered and the solvent was removed in vacuo to give a white solid. The white solid was triturated with Et_2O (100 mL) to given 1.30 g (87%) of the above-identified compound: mp 143°–144° C., $[\alpha]_D^{23}$ (c=1, MeOH)=+16.0°; ^1H NMR ($CDCl_3$) δ2.04 (s, $C(O)CH_3$), 3.38(s, OCH_3), 3.44 (dd, J=7.5, 9.0 Hz, CH H^1 OCH_3), 3.81 (dd, J=4.2, 9.0 Hz, CHH'OCH_3), 4.48 (d, J=5.7 Hz, $NHCH_2$), 4.52–4.58 (m, CH), 6.46 (br d, J=5.7 Hz, NH), 6.78 (br, s, NH), 7.25–7.37 (m, 5 Ph H), addition of excess (R)-(−)-mandelic acid to a $CDCl_3$ solution of the above-identified compound gave only one signal for the acetyl and ether methyl protons.

EXAMPLE 3

R-N-(3-Fluorobenzyl)2-Acetamide-3-Methoxypropionamide

(a) R-N-(3-Fluorobenzyl)-2-Acetamide-hydracrylamide

Utilizing the procedure of Example 2(a) with the following amounts of D-serine (5.26 g, 50 mmol), Ac_2O (5.7 mL, 60 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), isobutyl chloroformate (13.0 mL, 100 mmol) and substituting 3-fluorobenzylamine (11.8 mL, 100 mmol) for benzylamine, gave 4.20 g (33%) of the above compound as a white solid after purification: mp 137°–138° C.; $[\alpha]_D^{23}$ (c=1, MeOH)=+20.8°; Rf0.32 (10% MeOH—$CHCl_3$); IR (KBr) 3282, 3101, 2944, 1636, 1542, 1252, 1050, 779, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.87 (s,$C(O)CH_3$), 3.56–3.63 (m, CH_2OH), 4.29 (d, J=6.0 Hz, CH_2NH), 4.25–4.30 (m, CH), 4.95 (t, J=5.4 Hz, CH_2OH), 7.00–7.09 (m, 3 ArH), 7.29–7.30 (m, 1 ArH), 7.97 (d, J=8.1 Hz, NH), 8.44 (t, J=6.0 Hz, NH), addition of excess (R)-(−)-mandelic acid to a $CDCl_3$ solution of this product gave only one signal for the acetyl methyl portions; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)CH_3), 41.6 (CH_2N), 53.4 (CH), 61.7 (CH_2 OH), 113.3 (d, J_{CF}=20.0 Hz, (C_2' or C_4'), 113.6 (d, J_{CF}=20.7 Hz, C_2' or C_4'), 122.9 (C_6'), 130.1 (d, J_{CF}=8.2 Hz, C_5'), 142.6 (d, J_{CF}=7.0 Hz, C_1'), 162.3 (d, J_{CF}=241.4 Hz, C_3'), 169.6 ($C(O)CH_3$ or C(O)NH), 170.5 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (rel. intensity) 255 (M^++1, 100); M_r(+Cl) 255.113 54 [M^++1] (calcd. for $C_{12}H_{16}FN_2O_3$ 255.114 50); Anal. ($C_{12}H_{15}FN_2O_3$) C, H, N.

(b) (R)-(N-3-Fluorobenzyl)-2-Acetamide-3-methoxypropionamide

To the product of (a) (2.54 g, 10 mmol) in a stirred CH_3CN solution was successively added Ag_2O (11.59 g, 50 mmol) and MeI (6.2 mL, 100 mmol) at room temperature. The reaction mixture was stirred at room temperature for 2 days. The insoluble salts were filtered and the solvent was removed in vacuo to give a white solid which was triturated with Et_2O (100 mL) to give a crude product of the above identified compound. The product was further purified by flash chromatography on SiO_2 gel (10% MeOH—$CHCl_3$) to give 2.00 g (75%) of the above-identified compound: mp 150°–151° C.; $[\alpha]_D^{23}$ (c=1, MeOH)=+16.5° C.; R_f 0.50 (10% MeOH—$CHCl_3$); IR (KBr) 3287, 3072, 2928, 2883, 1634, 1548, 1256, 1142, 785 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.05 (s, $C(O)CH_3$), 3.40 (s, OCH_3), 3.44–3.47 (m, CHH'OCH_3), 3.81–3.85 (m, CHH'OCH_3), 4.41–4.50 (m, $NHCH_2$), 4.53–4.59 (m, CH), 6.42 (br s, NH), 6.81 (br s, NH), 6.93–7.05 (m, 3 PhH), 7.26–7.31 (m, 1 PhH); addition of excess (R)-(−)-mandelic acid to a $CDCl_3$ solution of the above identified compound gave only one signal for the acetyl methyl protons and ether methyl protons; ^{13}C NMR (DMSO-d_6) 22.8 ($C(O)CH_3$), 42.7 (CH_2N), 52.6 (CH), 58.9 (OCH_3), 72.0 (CH_2OCH_3), 114.0 (d, J_{CF}=21.5 Hz, C_2' and C_4'), 122.7 (C_6'), 129.9 (d, J_{CF}=7.7 Hz, C_5'), 140.6 (d, J_{CF}=6.8 Hz, C_1'), 162.9 (d, J_{CF}=244.4 Hz, C_3'), 170.2 ($C(O)CH_3$ or C(O)NH), 170.5 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (rel. intensity) 269 (M^++1, 100); M_r (+Cl) 269.129 31 [M^++1] (calcd for $C_{13}H_{18}FN_2O_3$ 269.130 15); Anal. ($C_{13}H_{17}FN_2O_3$) C, H, N.

EXAMPLE 4

(R)-N-(4-Fluorobenzyl)2-Acetamido-3-Methoxypropanamide

(a) (R)-N-(4-Fluorobenzyl)2-Acetamidohydracrylamide

Utilizing the procedure of Example 2(a) with the following amounts of D-serine (5.26 g, 50 mmol), Ac_2O (5.7 mL, 60 mmol), 4-methylmorpholine (11.0 mL, 100 mmol), and isobutyl chloroformate (13.0 mL, 100 mmol) and substituting 4-fluorobenzylamine (11.8 mL, 100 mmol) for benzylamine, the above-identified compound was prepared as a white solid after purification (4.08 g, 32%); mp: 169°–170° C.; $[\alpha]_D^{23}$ (c=1, MeOH)=+17.6°; R_f0.31 (10% MeOH—$CHCl_3$); IR (KBr) 3289, 3101, 3071, 2936, 1632, 1565, 1543 1508, 1214, 1053, 814 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.86 (s, $C(O)CH_3$), 3.56 (6, J=5.4 Hz, CH_2OH), 4.25 (d, J=6.0 Hz, CH_2NH), 4.25–4.29 (m, CH), 4.91 (t, J=5.4 Hz, CH_2OH), 7.08–7.14 (m, $2C_{2'H}$), 7.25–7.29 (m, $2C_{3'H}$), 7.93 (d, J=7.8 Hz, NH), 8.39 (d, J=6.0 Hz, NH), addition of excess (R)-(−)-mandelic acid to a $CDCl_3$ solution of the above-identified compound gave only one signal for the acetyl methyl protons; ^{13}C NMR (DMSO-d_6) 22.7 (C(O)CH_3), 41.3 (CH_2N), 55.3 (CH), 61.7 (CH_2OH), 114.8 (d, J_{CF}=21.8 Hz, $2C_3$'), 128.9 (d, J_{CF}=8.0 Hz, $2C_2$'), 135.6 (C_1'), 161.1 (d, J_{CF}=240.1 Hz, C_4'), 169.4 ($C(O)CH_3$ or C(O)NH), 170.3 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (rel. intensity) 255 (M^++1, 100); Mr(+Cl) 255.113 60 [M^++1] (calcd for $C_{12}H_{16}FN_2O_3$ 255.114 50); Anal. ($C_{12}H_{15}FN_2O_3$.0.2H_2O) C, H, N.

(b) R-N-(4-Fluorobenzyl)2-Acetamido-3-methoxypropanamide

Following the procedure of Example 3(b) to the product of Example 4(a) (2.54 g, 10 mmol) in a stirred CH_3CN solution (300 mL) was successively added) Ag_2O (11.59 g, 50 mmol) and MeI (6.2 mL, 100 mmol) at room temperature and then stirred for 7 days. The insoluble salts were filtered, and the solvent was removed in vacuo to given a white solid. The white solid was triturated with Et_2O (100 mL) to give a crude product. The crude product was further purified by flash column chromatography (10% MeOH—$CHCl_3$) to give 2.00 g (75%) of the above product; mp: 144°–145° C.; $[\alpha]_D^{23}$ (c=1, MeOH)=+12.0; R_f0.52 (10% MeOH—$CHCl_3$); IR (KBr) 3281, 3102, 3072, 2959, 1632, 1547, 1513, 1223, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.04 (s, C(O) CH_3), 3.38 (s, OCH_3), 3.39–3.46 (m, CHH'OCH_3), 3.80–3.84 (m, CHH'OCH_3), 4.44 (br d, J=5.4 Hz, CH_2NH), 4.48–4.56 (m, CH), 6.42 (br s, NH) 6.76 (br s, NH), 6.99–7.05 (m, 2 PhH), 7.21–7.31 (m, 2 PhH), addition of excess (R)-(−)-mandelic acid to a $CDCl_3$ solution of the above-identified product gave only one signal for the acetyl methyl portions and ether methyl portions, ^{13}C NMR ($CDCl_3$) 22.9 ($C(O)CH_3$), 42.6 (CH_2N), 52.5 (CH), 58.9 (OCH_3), 72.0 (CH_2OCH_3), 115.3 (d, J_{CF}=22.0 Hz, $2C_3$'), 129.0 (d, J_{CF}=6.9 Hz, $2C_2$'), 133.7

($C_{1'}$) 161.9 (d, J_{CF}=245.3 Hz, $C_{4'}$), 170.1 (C(O)CH_3 or C(O)NH), 170.4 (C(O)CH_3 or C(O)NH) ppm; MS (+Cl) (rel. intensity) 269 (M^++1, 100); M_r (+Cl) 269.129 66 [M^++1] (calcd for $C_{13}H_{18}FN_2O_3$ 269.130 15); Anal. ($C_{13}H_{17}FN_2O_3$) C, H, N.

EXAMPLE 5

N-Benzyl 2-Acetamide-3-Methoxypropionamide

(a) Cbz-(D) Serine (9)

D-Serine (5 g) was dissolved in water (85 mL). To this was added MgO (6 g), and ethyl ether (40 mL). The mixture was cooled in an ice bath to 0° C. To this ice-cold mixture was added slowly, dropwise benzylchloroformate (95%, 11 mL). Upon complete addition, the mixture was stirred at 0° C. (2 h) and then allowed to spontaneously warm to room temperature. Stirring was continued for an additional 30 minutes. The mixture was filtered and the filtrate washed with ethyl ether (2×25 mL). The aqueous layer was separated and cooled in an ice bath to 0° C. The pH of this ice-cold aqueous layer was carefully adjusted to 3.0 using 5N HCl. The acidified solution was stored in a refrigerator overnight. The white crystalline solid product was isolated by filtration, and dried in vacuo. The filtrate was extracted with ethylacetate (2×50 mL). The combined ethyl acetate extracts were dried (Na_2SO_4), filtered and evaporated in vacuo to obtain additional amounts of the white crystalline product. Total product obtained was 7.51 g (68%): mp 118°–120° C.

(b) Methyl-2-(Carbobenzyloxyamino)-3-Methoxypropionate (10)

To a solution of 9 (1.72 g, 7.21 mmol) in acetonitrile (150 mL) was added methyl iodide (10.23 g, 72.1 mmol, 4.5 mL) and silver(I)oxide (8.4 g, 36 mmol) and the mixture was stirred in the dark at room temperature for 24 hours. The insoluble salts and excess silver oxide were removed by filtration and the filtrate was evaporated in vacuo to obtain an oily residue which was subjected to flash column chromatography (silica gel and 5% MeOH—$CHCl_3$) to obtain pure 10 as a pale yellow oil (1.81 g, 94%): R_f (10% MeOH/$CHCl_3$) 0.75.

(c) 2-(Carbobenzyloxyamino)-3-Methoxypropionic Acid (11)

Compound 10 (0.58 g) was dissolved in 80% aqueous methanol (3.0 mL). To this solution was added anhydrous K_2CO_3 (0.5 g) and the reaction mixture was stirred at room temperature (8 hours). The methanol was evaporated in vacuo and the residue suspended in water (50 mL). The aqueous suspension was washed with ethyl ether (2×25 mL) and then acidified to pH 3.0 using 5N HCl. The acidified aqueous phase was extracted with ethyl acetate (3×25 mL). The ethyl acetate extracts were combined, dried (Na_2SO_4), filtered, and evaporated in vacuo to obtain pure 11 as a clear viscous oil (0.52 g, 95%): R_f0.30 (10% MeOH/$CHCl_3$).

(d) N-Benzyl 2-(Carbobenzyloxyamino)-3-Methoxypropionamide (12)

A solution of 11 (0.52 g, 2.04 mmol) in dry tetrahydrofuran (10 mL) was cooled to −78° C. in a dry ice-acetone bath under a N_2 atmosphere. To this was added via a dry syringe 4-methylmorpholine (0.34 mL, 3.06 mmol). After stirring for 5 minutes, isobutyl chloroformate (0.4 mL, 3.06 mmol) was added via dry syringe and then the mixture stirred for 5 minutes. This was followed by the addition of benzylamine (0.32 mL, 3.06 mmol). After stirring at −78° C. for 5 minutes, the reaction was allowed to warm to room temperature, and stirring was continued at room temperature (30 min). The hydrochloride salt of 4-methyl morpholine was removed from the reaction by filtration. The clear filtrate was evaporated in vacuo and the residue was triturated with ethyl ether (5.0 mL). The white crystalline product obtained was isolated by filtration after washing with small amounts of ether and air-dried (0.55 g, 78%): mp 112°–114° C., R_f 0.6 (10% MeOH/$CHCl_3$)

(e) N-Benzyl-2-Amino-3-Methoxypropionamide (13)

To a solution of 12 (122.8 mg, 0.36 mmol) in methanol (2.0 mL) was added 10% Pd—C (11 mg) and the mixture stirred at room temperature in the presence of H_2 gas for 75 min. Celite was added to the reaction mixture and the catalyst was removed by filtration. The clear filtrate was evaporated in vacuo to give pure 13 as a clear viscous oil (72 mg, 97%): R_f 0.30 (5% MeOH/$CHCl_3$).

(f) N-Benzyl-2-Acetamido-3-Methoxypropionamide

To a solution of 13 (0.20 g, 0.98 mmol) in dry THF (2.0 mL) is added pyridine (0.086 g, 1.08 mmol), and then acetic anhydride (0.2 g, 1.96 mmol) is added dropwise. The reaction is stirred at room temperature for 18 hours. The solvent is evaporated in vacuo and the residue purified by flash column chromatography to obtain the above compound as the R isomer.

COMPARATIVE EXAMPLE 1

Preparation of N-Acetyl-D,L-alanine-N'-benzylamide

Acetic anhydride (2.20 g, 0.022 mol) was slowly added to a methylene chloride solution (30 mL) of D,L-alanine-N-benzylamide (3.80 g, 0.021 mol) and allowed to stir at room temperature (3 h). The mixture was then successively washed with H_2O (15 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was recrystallized from CH_2Cl_2.

Yield: 2.50 g (54%). mp 139°–141° C.

^1H NMR (DMSO-d_6): δ1.22 (d, J=7.1 Hz, 3H), 1.84 (s,3H), 4.04–4.50 (m,3H), 7.26 (s,5H), 8.11 (br d, J=7.3 Hz, 1H), 8.42 (br t, J=6 Hz, 1H).

^{13}C NMR (DMSO-d_6): 18.2, 22.4, 41.9, 48.2, 126.5, 126.9, 128.1 139.4, 168.9, 172.4 ppm.

IR ($CHCl_3$) 3440, 3300, 3005, 1660, 1515 cm^{-1}.

Mass spectrum (CI mode), m/e: 221 (P+l); mol wt. 220.1208 (calculated for $C_{12}H_{16}N_2O_2$, 220.1212).

COMPARATIVE EXAMPLES 2 AND 3

Preparation of N-Acetyl D and L-amino acid N-benzylamides

General procedure: The D or L amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (18 h) and then concentrated to dryness. The residue was crystallized from chloroform/hexane.

COMPARATIVE EXAMPLE 2

N-Acetyl-D-alanine-N'-benzylamide

Yield: 1.36 g (56%). mp 139°–141° C. $[\alpha]_D^{23}$=+36.2 (c 2.5, MeOH).

^{1}H NMR (80 MHz, DMSO-d_6): δ1.25 (d, J=7.1 Hz, 3H), 1.86 (s, 3H), 4.04–4.50 (m, 1H), 4.30 (d, J=6.0 Hz, 2H), 7.26 (s, 5H), 8.09 (d, J=7.3 Hz, 1H), 8.40 (t, J=6.0 Hz, 1H).

^{13}C NMR (80 MHz, DMSO-d_6): 18.3, 22.5, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.2, 172.5 ppm.

IR (KBr): 3290, 1635 (br), 1540, 1455, 700, 695 cm^{-1}.

Mass spectrum, m/e (relative intensity): 221 (30), 114 (20), 106 (40), 91 (80), 87 (100), 77 (5), 72 (20), 65 (5).

Elemental analysis calculated for $C_{12}H_{16}N_2O_2$ 65.42% C; 7.34% H; 12.72% N. Found 65.31% C; 7.28% H; 12.63% N.

COMPARATIVE EXAMPLE 3

N-Acetyl-L-alanine-N'-benzylamide

Yield: 1.11 g (46%). mp 139°–142° C. $[\alpha]_D^{23}$=35.3 (c 2.5, MeOH). ^{1}H NMR (80 MHz, DMSO-d_6): δ1.23 (d, J=7.2 Hz, 3H), 1.86 (s, 3H), 4.26–4.35 (m, 1H), 4.29 (d, J=5.8 Hz, 2H), 7.22–7.33 (s,5H), 8.10 (d, J=7.4 Hz, 1H), 8.42 (t, J=5.8 Hz, 1H).

^{13}C NMR (80 MHz, DMSO-d_6): 18.3, 22.6, 42.0, 48.4, 126.7, 127.0 (2C), 128.3 (2C) 139.5, 169.2, 172.6 ppm.

IR (KBr): 3290, 1635 (br), 1545, 1450, 700, 695 cm^{-1}.

Mass spectrum, m/e (relative intensity): 221 (40), 114 (40), 106 (80), 106 (80), 91 (75), 87 (100), 77 (5), 72 (15), 65 (5).

Elemental analysis calculated for $C_{12}H_{16}N_2O_2$ 65.42% C; 7.34% H; 12.72% N. Found 65.58% C; 7.32% H; 12.43% N.

COMPARATIVE EXAMPLE 4

Preparation of D,L-2-Acetamido-N-benzyl-2-methoxyacetamide

To a methanolic solution (180 mL) of methyl 2-acetamide-2-methoxyacetate (8.73 g, 54 mmol) was rapidly added benzylamine (8.68 g, 8.80 mL, 81 mmol) and then the mixture was stirred at 50° C. (3 days) during which time a beige precipitate appeared. The solvent was removed in vacuo and the resulting precipitate was recrystallized from tetrahydrofuran (2×) to given 7.67 g (32%) of the desired product as beige crystals: R_f 0.35 (95:5 chloroform/methanol). mp 145°–146° C.

^{1}H NMR (300 MHz, $CDCl_3$): δ2.06 (s, CH_3CO), 3.37 (2,CH_{3O}), 4.40–4.35 (m, CH_2), 5.52 (d, J=8.7 Hz, CH), 7.12 (d, J=8.7 Hz, NH), 7.20–7.40 (m, Ph, NH).

^{13}C NMR (300 MHz, $CDCl_3$): 23.03 (CH_3CO), 43.51 (CH_2), 55.84 (CH_{3O}), 78.94 (CH), 127.62 (C_4"), 127.70 ($2C_2$" or $2C_3$'"), 128.70 ($2C_2$ or $2C_3$'), 137.45 (C_1"), 166.91 ($COCH_3$), 171.57 (CONH) ppm.

IR (KBr): 1260, 1825 (br), 1550, 1505, 1435, 1390, 1370, 1230, 1120, 1050 935, 890, 690 cm^{-1}.

Mass spectrum, m/e (relative intensity): 237 (1), 205 (2), 177 (2), 163 (4), 146 (1), 134 (1), 121 (2), 106 (26), 102 (98), 91 (95), 77 (13), 61 (100). Elemental analysis calculated for $C_{12}H_{16}N_2O_3$ 61.00% C; 6.83% H; 11.86% N. Found 60.91% C; 6.85% H; 11.66% N.

COMPARATIVE EXAMPLES 5–7

Synthesis of Unsubstituted and Substituted-α-Acetamido-N-benzyl-2-furanacetamides

General Procedure

4-Methylmorpholine (1 equiv) was added to a solution of α-acetamido-2-furanacetic acid (1 equiv) in dry tetrahydrofuran (75 mL/10 mmol) at −10° to −15° C. under N_2. After stirring (2 min.), isobutyl chloroformate (1 equiv) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for 2 additional minutes and then a solution of the substituted benzylamine (1 equiv) in tetrahydrofuran (10 mL/10 mmol) was added over 5 min. at −10° to −15° C. The reaction mixture was allowed to stir at room temperature for 5 min. and then the 4-methylmorpholine hydrochloride salt filtered. The organic layer was concentrated in vacuo, and the residue was triturated with ethyl acetate, and the remaining white solid filtered. Concentration of the ethyl acetate layer led to additional amounts of the white solid. The desired product was purified by either recrystallization or flash chromatography of the combined solid material.

COMPARATIVE EXAMPLE 5

(D,L)-α-Acetamido-N-benzyl-2-furanacetamide

Benzyl amine (0.27 g, 2.56 mmol) and racemic α-acetamido-2-furanacetic acid (0.47 g, 2.56 mmol) gave the desired compound. The product was recrystallized from ethyl acetate to give a white solid.

Yield: 0.46 g (65%) R_f 0.30 (98:2 chloroform/methanol). mp 177°–178° C.

^{1}H NMR (DMSO-d_6) δ1.90 (s, CH_3), 4.31 (d, J=6.0 Hz, CH_2), 5.58 (d, J=8.1 Hz, CH), 6.27–6.33 (m, C_3H), 6.40–6.44 (m, C_4H), 7.20–7.36 (m, 5 PhH), 7.60–7.64 (m, C_5H), 8.57 (d, J=8.1 Hz, NH), 8.73 (t, J=6.0 Hz, NH).

COMPARATIVE EXAMPLE 6

(D)-(−)α-Acetamido-N-benzyl-2-furanacetamide

Starting with D-α-acetamido-2-furanacetic acid (2.45 g, 13.38 mmol) and benzylamine (1.43 g, 13.38 mmol), the desired product was obtained. Yield: 2.54 g (70%). The product was further recrystallized from ethyl acetate to give the title compound.

Yield: 2.30 g mp 196°–197° C. $[\alpha]^{26}$D[c=1, MeOH]= 78.30. Addition of R(−)-mandelic acid to a $CDCl_3$ solution the product gave only one signal for the acetamide methyl protons. Mass spectrum, m/e (relative intensity) 272 (M+, 2), 184 (2), 165 (2), 140 (8), 139 (88), 138 (34), 97 (46), 96 (100), 91 (63).

Elemental analysis: calculated: 66.16% C; 5.92% H; 10.29% N. Found: 66.09% C; 6.01% H; 10.38% N.

COMPARATIVE EXAMPLE 7

(L)-(+)-α-Acetamido-N-benzyl-2-furanacetamide

L-α-acetamido-2-furanacetic acid (2.83 g, 15.46 mmol) and benzylamine (1.65 g, 15.4 mmol) gave 3.80 g of the enriched desired product. ^{1}H NMR analysis with R(−)-mandelic acid showed that it was greater than 80% enriched in the title compound. The pure L-enantiomer was obtained by recrystallization from absolute ethanol.

Yield: 1.60 g. mp 196°–197° C. $[\alpha]^{26}D$[c=1, MeOH]=+79.0°.

Mass spectrum, m/e (relative intensity) 273 (M^++1,3) 229 (2), 214 (2), 184 (1), 165 (7), 157 (4), 140 (33), 139 (100), 138 (95), 97 (98), 96 (100), 91 (98).

Elemental analysis: calculated: 66.16% C; 5.92% H; 10.29% N. Found: 65.89% C; 5.86% H; 10.42% N.

COMPARATIVE EXAMPLE 8

Synthesis of N-Benzyl 2-Acetamidohydracrylamide

To an anhydrous THF solution (400 mL) of methyl-α-acetamido-N-benzylmalonamate (14.4 g, 54.5 mmol) was successively added dry LiCl (4.62 g, 109 mmol), $NaBH_4$ (4.13 g, 109 mmol) and EtOH (200 mL). The reaction mixture was stirred at room temperature (5h). The suspension was concentration in vacuo. After continuous extraction (12h) of the product using $CHCl_3$ (1000 mL) and H_2O (250 mL), the organic layer was collected, dried (Na_2SO_4), and removed in vacuo to give a crude white solid. The crude product was triturated with Et_2O (500 mL) to give 11.45 g (89%) of the above compound: mp 201°–203° C.; R_f0.40 (10% MeOH—$CHCl_3$); IR (KBr) 3287, 3085, 2969, 2859, 1648, 1552, 1456, 1055, 697 cm^-; ^1H NMR (DMSO-d_6) 51.88 (s, $C(O)CH_3$), 3.59 (dd, J=5.7 Hz, 5.7 Hz, CH_2O), 4.19–4.35 (m, CH_2NH, CH), 4.92 (t, J=5.7 Hz, OH), 7.10–7.40 (m, 5 PhH), 7.94 (d, J=5.7 Hz, NH), 8.38 (t, J=5.7 Hz, NH); ^{13}C NMR (DMSO-d_6) 22.2 ($C(O)CH_3$), 41.6 (CH_2N), 54.9 (CH), 61.3 (CH_2OH), 126.2 ($C_{4'}$), 126.5 ($2C_{2'}$ or $2C_{3'}$), 127.7 ($2C_{2'}$ or $2C_{3'}$), 138.9 ($C_{1'}$), 169.1 ($C(O)CH_3$ or C(O)NH), 169.9 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (relative intensity) 237 (M^++1, 100), 219 (9); M_r(+Cl) 237.123 88 [M^++1] (calcd for $C_{12}H_{17}N_2O_3$ 237.123 92); Anal. ($C_{12}H_{16}N_{21}$ $_{O3}$) C, H, N.

COMPARATIVE EXAMPLE 9

Synthesis of N-Benzyl 2-Acetamido-3-methoxypropionamide(racemic mixture)

To an CH_3CN solution (500 mL) of the product of Comparative Example 8 (2.36 g, 10 mmol) was successively added Ag_2O (11.59 g, 50.0 mmol) and CH_3I (6.23 mL, 100 mmol) at room temperature and then the reaction mixture was stirred at room temperature (4 d). The insoluble salts were filtered, and the solvent was removed in vacuo to give a white solid. The residue was triturated with Et_2O (50 mL) to give 2.10 g (84%) of the above-identified compound: mp 121°–122° C.; R_f0.47 (10% MeOH—$CHCl_3$); IR (KBr) 3290, 3087, 2924, 2878, 2820, 1637, 1548, 1139, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.04 (s,$C(O)CH_3$), 3.38 (s, OCH_3), 3.43 (dd, J=7.8, 9.0 Hz, $CHH'OCH_3$), 3.82 (dd, J=4.2, 9.0 Hz, $CHH'OCH_3$), 4.48 (d, J=6.0 Hz, $NHCH_2$), 4.51–4.57 (m,CH), 6.43 (br d, J=5.4 Hz, NH), 6.74 (br s, NH), 7.25–7.37 (m, 5 PhH); ^{13}C NMR ($CDCl_3$) 23.2 ($C(O)CH_3$), 43.5 (CH_2N), 52.4 (CH), 59.1 (OCH_3), 71.7 (CH_2OCH_3), 127.4 ($C_{4'}$ and $2C_{2'}$ or $2C_{3'}$), 128.7 ($2C_{2'}$ or $2C_{3'}$), 137.8 ($C_{1'}$), 170.0 ($C(O)CH_3$ or C(O)NH), 170.3 ($C(O)CH_3$ or C(O)NH) ppm; MS (+Cl) (relative intensity) 251 (M^++1, 100), 219 (100); M_r(+Cl) 251.139 39 [M^++1] (calcd for $C_{13}H_{19}N_2O_3$ 251.139 57); Anal. ($C_{13}H_{18}N_2O_3$) C, H, N.

COMPARATIVE EXAMPLE 10

(S)-N-Benzyl 2-Acetamidohydracrylamide

To a stirred AcOH (20 mL) suspension of L-serine (2.63 g, 25 mmol) was added Ac_2O (2.5 mL, 26.3 mmol) and then the reaction suspension was stirred at room temperature (24h). The AcOH was removed in vacuo to given an oily residue, and then THF (150 mL) was added to the residue. The THF suspension was cooled to −78° C. under N_2 and 4-methylmorpholine (5.5 mL, 50 mmol) was added. After stirring (2 min.), isobutyl chloroformate (6.5 mL, 50 mmol) was added leading to the precipitation of white solid. The reaction was allowed to proceed for two additional minutes and then benzylamine (5.5 mL, 50 mmol) was added at −78° C. The reaction mixture was allowed to stir at room temperature (30 min.) and then the 4-methylmorpholine hydrochloride salt was filtered. The organic layer was concentrated in vacuo. The product was purified by flash column chromatography on SiO_2 gel (10% MeOH—$CHCl_3$) to given 2.20 g (37%) of the above product as a white solid: mp 146°–147° C.; $[\alpha]_D^{23}$ (c=1, MeOH)=−21.50; ^1H NMR (DMSO-d_6) δ1.86 (s, $C(O)CH_3$), 3.57 (dd, J=5.1 Hz, 5.1 Hz, CH_2O), 4.25–4.32 (m, CH_2NH, CH), 4.91 (t, J=5.1 Hz, OH), 7.20–7.33 (m, 5 PhH), 7.93 (d, J=8.1 Hz, NH), 8.37 (t, J=5.7 Hz, NH), addition of excess (R)-(−) mandelic acid to a $CDCl_3$ solution of the above-identified compound gave only one signal for the acetyl methyl protons.

COMPARATIVE EXAMPLE 11

(S)-N-Benzyl 2-Acetamido-3-methoxypropionamide

To a stirred CH_3CN solution (300 mL) of the compound produced in Comparative Example 10 (1.18 g, 5 mmol) was successively added Ag_2O (5.80 g, 25 mmol) and MeI (3.1 mL, 10 mmol) at room temperature. The reaction mixture was stirred at room temperature (4 d). The insoluble salts were filtered, and the solvent was removed in vacuo to give a white solid. The white solid was triturated with Et_2O (100 mL) to give 1.00 g (80%) of the above-identified compound: mp 143°–144° C. $[\alpha]^{23}D$ (c=1, MeOH)=−16.4°; ^1H NMR ($CDCl_3$) δ2.03 (s, $C(O)CH_3$), 3.38 (s, OCH_3), 3.43 (dd, J=7.5, 9.0 Hz, $CHH'OCH_3$), 3.81 (dd, J=4.2, 9.0 Hz, $CHH'OCH_3$), 4.47 (d, J=5.7 Hz, $NHCH_2$), 4.52–4.59 (m,CH), 6.48 (br d, J=6.0 Hz, NH), 6.81 (br s, NH), 7.25–7.37 (m, 5 Ph), addition of excess (R)-(−)-mandelic acid to a $CDCl_3$ solution of the above-identified compound gave only one signal for the acetyl methyl and ether methyl protons.

COMPARATIVE EXAMPLE 12

(R)-N-Benzyl 2-Acetamidohydracylamide

This compound was prepared in accordance with the procedures described in Examples 1 and 2.

COMPARATIVE EXAMPLE 13

N-Acetyl-D,L-phenylglycine-N-benzylamide

This compound was prepared in accordance with the procedure described in U.S. Pat. No. 5,378,729, the contents of which are incorporated by reference. The D,L-phenylglycine amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4–6h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 2.05 g (66%) mp 202°–203° C.

^1H NMR (DMSO-d_6) : δ1.91 (s, 3H) , 4.27 (d, J=5.6 Hz, 2H), 5.50 (d, J=7.9 Hz, 1H), 7.21 (s, 5H), 7.36 (s, 5H), 8.38–8.86 (m, 2H).

^{13}C NMR (DMSO-d_6): 22.3, 42.0, 56.3, 126.6 (2C), 127.0, 127.1 (2C), 127.4 (2C), 128.1 (2C), 138.9, 139.0, 168.9, 169.9 ppm.

IR (KBr): 3020, 1635, 1580, 1540, 1450, 1265, 745, 690 cm^{-1}.

Mass spectrum, m/e (relative intensity): 283(20), 264(21), 149(100), 131(20), 118(34), 106(92), 91(70), 79(56), 77(54), 65(45), 51(37).

Elemental analysis Calculated for $C_{17}H_{18}N_2O_2$ 72.31% C; 6.44% H; 9.92% N. Found 72.49% C; 6.47% H; 9.89% N.

The compounds of the present invention are useful for the treatment of central nervous disorders, such as epilepsy, nervous anxiety , psychosis, insomnia and the like in animals, e.g., mammals, such as man, in need thereof. They exhibit excellent anti-convulsant activity, and of course and can thus be administered for short term treatment. Moreover, the compounds of the present invention have the added advantage of being useful in drug regimes for long-term treatment. The compounds of the present invention are substantially non-toxic, exhibiting minimal toxicity, if any, to the treated animal, as shown below in the pharmacology section.

PHARMACOLOGY

Compounds were screened for anticonvulsant activity in both male albino Carthworth Farms No. 1 mice (ip route) and male albino Sprague Dawley rats [oral (po) route]. Activity was established using the electrical (maximal electroshock or MES) test. In the MES test, a drop of electrolyte solution with anesthetic (0.5% butacaine hemisulfate in 0.9% sodium chloride) was used in the eyes of the animals prior to positioning the corneal electrodes and delivery of current. A 60 cycle alternating current was administered for 0.2 sec. in both species, 50 mA in mice and 150 mA in rats. Protection endpoints were defined as the abolition of the hind limb tonic extensor component of the induced seizure. In mice, effects of compounds on forced spontaneous motor activity were determined using the rotorod test. The inability of animals to maintain their balance for 1 min. on a 1 inch diameter knurled rod at 6 rpms in 3 successive trials demonstrated motor impairment. Normally under these conditions, mice maintain their balance almost indefinitely. In rats, motor impairment is assessed by observing for overt evidence of ataxia, abnormal gait and stance, and/or loss of placing response and muscle tone. In the mouse identification screening study all compounds were given at three dose levels (30, 100, 300 mg/kg) and two time periods (0.5 hours, 4 hours). Typically, in the MES seizures test one animal was tested at 30 mg/kg and 300 mg/kg, and three animals at 100 mg/kg. In the rotored toxicity test four animals were tested at 30 mg/kg, and 300 mg/kg, and eight animals at 100 mg/kg. If activity was found at 30 mg/Kg, then lower dosages were used to find the ED_{50} values.

The quantitative determination of the median effective (ED_{50}) and toxic doses (TD_{50}) was conducted at previously calculated times of peak effect. Groups of at least eight animals were tested using different doses of test compound until at least two points wee determined between 100 and 0% protection and minimal motor impairment. The dose of candidate substance required to produce the defined endpoint in 50% of the animals in each test and the 95% confidence interval was calculated.

TABLE 1

Physical and Pharmacological Data for Functionalized N-Benzyl 2-Acetamidopropionamide Stereoisomers of the formula $ArCH_2NHC(O)CH(R^2)NHC(O)CH_3$

					mice (ip)[b]			rat (po)[f]		
No.	Stereobem.	R^2	Ar	m p[a]	MES,[c] ED_{50}	tox,[d] TD_{50}	PI[e]	MES,[c] ED_{50}	tox,[d] TD_{50}	PI[e]
Comp. Ex. 1	(R, S)	CH_3	Ph	138–139	76.5 [1] (66.6–89.0)	454 [0.5] (417–501)	5.9	24.2 [1] (32.0–71.8)	_[b]	>20.8
Comp. Ex. 2	(R)	CH_3	Ph	139–141	54.8 [0.5] (50.3–59.7)	2.14 [0.5] (148–262)	3.9	28.4 [4] (22.4–35.0)	_[b]	>35.2
Comp. Ex. 3	(S)	CH_3	Ph	139–142	548 [0.5] (50.3–59.7)	841 [0.5] (691–954)	1.5	_[i]	_[i]	[i]
Comp. Ex. 9	(R, S)	CH_2OCH_3	Ph	121–122	8.3 [0.5] (7.9–9.8)	42.9 [0.25] (38.1–46.8)	5.2	3.8 [2] (2.9–5.5)	386.8 [1] (316.0–514.6)	101.8
Ex. 1, 2	(R)	CH_2OCH_3	Ph	143–144	4.5 [0.5] (3.7–5.5)	26.8 [0.25] (25.5–28.0)	6.0	3.9 [0.5] (2.6–6.2)	>500 [0.5]	>128.2
Comp. Ex. 11	(S)	CH_2OCH_3	Ph	143–144	>100, <300	>300		>30	>30	[i]
Comp. Ex. 8	(R, S)	CH_2OH	Ph	201–203	>100, 300	>300		_[i]	_[i]	[i]
Comp. Ex. 12	(R)	CH_2OH	Ph	148–149	53.4 [2] (37.5–67.3)	>500 [2]	>9.4	_[i]	_[i]	[i]
Ex. 3	(R)	CH_2OCH_3	Ph (m-F)	150–151	6.9 [0.25] (6.1–8.0)	46.3 [0.25] (40.4–54.5)	6.7	6.9 [0.5] (4.3–9.9)	>396 [0.5]	>57.7
Ex. 4	(R)	CH_2OCH_3	Ph (p-F)	144–145	4.2 [0.5] (3.5–5.1)	27.8 [0.25] (22.4–33.5)	6.6	2.6 [2] (1.9–3.6)	>125, <250	[i]
Comp. Ex. 4	(R, S)	OCH_3	Ph	145–146	98.30	>100 <300	>1, <3	_[i]	[i]	[i]
Comp. Ex. 6	(R)	furyl	Ph	190–197	3.3	23.8	>.2	_[i]	_[i]	[i]
Comp. Ex. 7	(S)	furyl	Ph	196–197	>25.	>200	_[i]	_[i]	[i]	[i]

TABLE 1-continued

Physical and Pharmacological Data for Functionalized N-Benzyl 2-Acetamidopropionamide Stereoisomers of the formula $ArCH_2NHC(O)CH(R^2)NHC(O)CH_3$

					mice (ip)[b]			rat (po)[f]		
No.	Stere obem.	R^2	Ar	m p[a]	MES,[c] ED_{50}	tox,[d] TD_{50}	PI[e]	MES,[c] ED_{50}	tox,[d] TD_{50}	PI[e]
Comp. Ex. 5	(R, S)	furyl	Ph	178–179	10.3	~40	>3.9	_[i]	_[i]	[i]
Comp. Ex. 13	(D, L)	Ph	Ph	112–115	20.3	96.92	4.77	48.3	>1000	>20.7

[a]Melting points (° C.) are uncorrected.
[b]The compounds were administered interperitoneally. ED_{50} and TD_{50} values are in mg/kg. Numbers in parentheses are 95% confidence intervals. The dose effect data was obtained at the "time of peak effect" [indicated in hours in the brackets].
[c]MES = maximal electroshock seizure test.
[d]Tbx = neurologic toxicity determined from rotorod test.
[e]PI = protective index (TD_{50}/MES Ed_{50})
[f]The compounds were administered orally.
[g]No alaxia observed up to 1000 mg/kg.
[i]Data not available

The compounds of the present invention were compared with respect to their efficacy and toxicity and PI values to compounds having a structural similarity with the difference being the substituent at R^2. The protocols for these compounds is as described hereinabove.

The results thereof are provided in Table I.

As clearly shown by the above data, the R enantiomers of the present invention have quite potent anticonvulsant activity. The inventor has also found that the R stereoisomer is unexpectedly more potent than the corresponding S stereoisomer and the racemic mixture.

The data in the table clearly demonstrate that the efficacy of the comparative examples are significantly less than those of the present invention. Only the 2-furyl derivative in the Table shows comparable potency.

In addition, the compounds of the present invention have relatively low neurological toxicity, considering the efficacy thereof. In fact, as clearly shown by the data, the neurological toxicity is significantly lower in rats in which the compounds were administered orally than in the mice in which the compounds were administered intraperitoneally. In fact, in rats, the neurological toxicity of the compounds of the present invention is very low.

The PI values of the compounds of the present invention are quite high in the mice model in which the compounds were administered intraperitoneally and especially in the rat model in which the compounds were administered orally. Of the compounds tested, the PI values of the compounds of the present invention are generally higher than that of the comparative examples, except for the compound in which R^2 is CH_2OH. However, the efficacy of this latter compound is significantly less than that of compounds of the present invention.

It is important to place the data in the table in proper perspective. Looking at the data, it is quite apparent that the compounds of the present invention exhibit an excellent drug profile. On the other hand, based upon the data, except for the furyl derivatives, the other comparative compounds are significantly inferior drugs relative to the compounds of the present invention. Although in some cases, the neurological toxicity of the compounds of the comparative examples is low and the PI value is satisfactory, the data cannot be viewed in a vacuum. It is preferred that the drug not have a low potency, even if it has a low neurological toxicity. After all, the objective is to administer as little drug as possible to obtain an efficacious result; the more drug administered to achieve a particular efficacious result, the greater will be the risk that the drug would have other effects, some of which are adverse, on other bodily systems of the patient. Thus, except for the furyl derivatives, based upon the data in the table the other comparative examples have a significantly poorer drug profile relative to the compounds of the present invention.

There is thus still another factor which must be taken into consideration relating to the toxicity of the drug when administered for extended periods to the animal. Obviously, even if the drug has excellent anti-convulsant activity and an excellent PI ratio, the drug will not be useful if the drug is toxic upon chronic dosing to the patient. In the pharmaceutical industry relating to anti-convulsants, one of the standards utilized to measure a drug's toxicity to the animal is liver toxicity. The objective is to find a drug having a relatively low or substantially minimal liver toxicity.

Based upon the above data, both the furyl derivative and the compounds of the present invention have an excellent drug profile; and both could be used in acute administration. However even though the furyl compound is quite active, as will be shown hereinbelow, the furyl compound is more toxic to the animal, making it considerably less undesirable for chronic administration than the compounds of the present invention. On the other hand, the compounds of the present invention as shown hereinbelow are significantly less toxic than the furyl compound, and in fact exhibit little, if any, toxicity to the animal. Thus, the compounds of the present invention are useful for administration to the treated animal for an extended period.

The following experiments measure the effect of a representative compound of the present invention on the liver. The drug utilized is the compound of Example 1, i.e., R-N-Benzyl-2-Acetamide-3-methoxypropionamide, hereinafter referred to as BAMP.

I. Short term liver study

The protocol is as follows:

Four groups of 8 rats each were treated via p.O. administration daily for 4 days with vehicle (groups 1 and 2), or 3.9 mg/kg of the compound of Example 1 (group 3) or 100 mg/kg of the compound of Example 1 (group 4). On day 5, animals in groups 2, 3 and 4 received 3.9 mg/kg of compound 1 (hereinafter "BAMP") and those in group 1 received another dose of the vehicle.

To verify that the drug was effective, all groups were tested at the time of peak effect (TPE) for drug efficacy against MES-induced tonic extension, as described hereinabove.

Following the MES test, animals in group 4 received 96.1 mg/kg dose of the compound of Example 1, a dose equal to the difference between the ED_{50} and 100 mg/kg. On day 6, all groups were tested for sleep time response (time from loss to or regaining, of righting reflex) to a standard dose 100 mg/kg, i.p. of hexobarbital. The hexobarbital sleep time provides an assessment of hepatic drug metabolism. Following the performance of this test, all animal groups received the same treatment as they received on day 1. Day 7 had a similar dosing allocation except that group 2 received 100 mg/kg of BAMP. On days 8 and 9, four rats from each of the four groups were euthanized. Blood was collected in cooled tubes, allowed to clot, and then centrifuged to separate RBCs (red blood cells). The serum was frozen at -70° until serum alanine aminotransferase (sALT) activity, indicative of potential liver damage, was determined. The livers were perfused in situ with ice cold saline, blotted dry, weighed, homogenized in 0.25M sucrose and centrifuged to separate endoplasmic reticulum (i.e., macrosomes) and cytosol.

The protein concentration of both of these subcellular fractions was determined by the Lowry method described in Lowry, et al., in J. Biol Chem. 193, 265–275, (1951) and the yield of microsomal protein calculated. The protein concentration of these two subcellular fractions provide the basis for calculation of all enzyme concentrations and activities.

Changes in a wide range of drug metabolizing enzymes known to be variously altered by drug treatments were sought. Both microsomal and cytosolic Phase I (cytochrome P450 catalyzed oxidations and quinone oxidoreductase activity, respectively) and microsomal (glucuronidation) and cytosolic (glutathione and sulfate conjugation) Phase II conjugation reactions were evaluated, in accordance with the procedure described in Arch Biochem. Biophys, 143, 318–329 (1971), the contents of which are incorporated by reference. BAMP showed no evidence of causing liver necrosis. Collectively, the results obtained from a battery of liver enzyme studies suggest that the liability for serious drug-drug interactions and liver toxicity is relatively low for this compound.

Since the compound showed minimal liver toxicity in a 48 hours study, a much longer study was performed over 30 days.

The methodology is as follows:

II. Five groups of Crl:CD® BR Charles River rats were each exposed to BAMP or a control substance (0.5% methylcellulose [400 Cps] aqueous solution in distilled water) according to the following dosage schedule:

Group 1—vehicle control (10 males, 10 females), 0 mg/kg/day

Group 2—low (10 males, 10 females), 10 mg/kg/day

Group 3—mid low (10 males, 10 females), 30 mg/kg/day

Group 4—mid high (10 males, 10 females), 100 mg/kg/day

Group 5—high (10 males, 10 females), 300 mg/kg/day

Exposure was by oral gavage, once daily, for a period of at least 30 consecutive days, after which all animals were sacrificed for pathologic evaluation.

All animals were weighed once prior to initiation of dosing and weekly thereafter. Food-fasted (overnight) blood samples for clinical chemistry and hematology were collected at termination. Blood samples were collected from the orbital venous plexus using carbon dioxide (mixed with oxygen) as an anesthetic.

All animals were sacrificed, at the appropriate time, by exsanguination, under barbiturate anesthesia, and all were subjected to a necropsy examination.

Clinical observations were reviewed at necropsy, and all grossly observed abnormalities were entered directly into the computerized data collection system. Adrenals, brain with brainstem, heart, kidneys, liver, ovaries, pituitary, testes with epididymides, and thyroid with parathyroids were weighted from each animal. The pituitary and thyroid with parathyroids were weighed after fixation and all of the other organs were weighed at the time of necropsy. The changes in the weight of the liver is depicted in Table 3.

As required by the protocol, histologic evaluations were conducted on liver only from all animals of Groups 1 (control) and 5 (high). All histologic findings were entered directly into the computerized data capture system. Lesions were graded as to relative severity or degree of involvement (1=minimal, 2=slight, 3=moderate, 4=moderately severe, 5=severe). In general, minimal represents the least consistently recognizable degree of any given histoniorphologic alteration, while severe would represent the most extreme degree reasonably possible, with the other three grades occupying a continuum between the two extremes. The grades are subjective, comparative evaluations, based on morphology alone and are not intended by themselves to imply any degree of functional impairment.

Results

Gross Findings—There were few gross abnormalities reported. All were frequently encountered in normal populations of rats of this strain and age; none were suggestive of any effect of treatment. The data is found in Table 2.

TABLE 2

30-DAY RANGE-FINDING ORAL TOXICITY STUDY OF BAMP IN RATS
GROSS PATHOLOGY INCIDENCE SUMMARY
TABLE INCLUDES:
SEX = ALL; GROUP = ALL; WEEKS = ALL
DEATH = ALL; SUBSET = ALL

		NUMBER OF ANIMALS AFFECTED									
	SEX:	MALE					FEMALE				
ORGAN AND KEYWORD(S) OR PHRASE	GROUP: / NUMBER:	1 / 10	2 / 10	3 / 10	4 / 10	5 / 10	1 / 10	2 / 10	3 / 10	4 / 10	5 / 10
PARATHYROID (PT)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
	NOT REMARKABLE:	10	10	10	10	10	10	10	10	10	10
ESOPHAGUS (ES)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
	NOT REMARKABLE:	10	10	10	10	10	10	10	10	10	10

TABLE 2-continued

30-DAY RANGE-FINDING ORAL TOXICITY STUDY OF BAMP IN RATS
GROSS PATHOLOGY INCIDENCE SUMMARY
TABLE INCLUDES:
SEX = ALL; GROUP = ALL; WEEKS = ALL
DEATH = ALL; SUBSET = ALL

		NUMBER OF ANIMALS AFFECTED									
	SEX:	MALE					FEMALE				
ORGAN AND KEYWORD(S) OR PHRASE	GROUP: / NUMBER:	1 / 10	2 / 10	3 / 10	4 / 10	5 / 10	1 / 10	2 / 10	3 / 10	4 / 10	5 / 10
TRACHEA (TR)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
	NOT REMARKABLE:	10	10	10	10	10	10	10	10	10	10
LUNG (LU)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
	NOT REMARKABLE:	10	10	10	10	10	10	10	10	10	10
HEART (HT)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
	NOT REMARKABLE:	9	10	10	10	10	10	10	10	10	10
ENLARGED		1	0	0	0	0	0	0	0	0	0
SPLEEN (SP)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
	NOT REMARKABLE:	10	10	10	10	10	10	10	10	10	10
LIVER (LI)	NUMBER EXAMINED:	10	10	10	10	10	10	10	10	10	10
	NOT REMARKABLE:	10	10	10	10	9	10	10	10	10	10
ENLARGED		0	0	0	0	1	0	0	0	0	0

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Histopathology—All were of the kinds frequently encountered in normal populations of rats in this strain and age. None presented in a dropwise pattern suggestive of a treatment effect.

TABLE 3

30 DAY RANGE-FINDING ORAL TOXICITY STUDY OF BAMP IN RATS
ORGAN WEIGHT DATA
TABLE INCLUDES:
SEX = ALL; GROUP = ALL; WEEKS = ALL
DEATH = ALL; SUBSET = ALL
LIVER

SEX	DOSE GROUP	TERMINAL BODY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO RT
M	1				
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	356.3	11.76	3.323	5.760
	STANDARD DEV:	42.8	1.34	0.350	0.577
M	2				
	NUMBER IN GROUP:	30	10	10	10
	MEAN:	342.0	11.10	3.248	5.388
	STANDARD DEV:	26.6	0.96	0.161	0.391
M	3				
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	349.9	11.48	3.278	5.619
	STANDARD DEV:	21.4	1.26	0.265	0.666
M	4		100 mg/kg/day x 30 days		
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	351.5	11.79	3.351	5.702
	STANDARD DEV:	29.3	1.38	0.223	0.725
M	5		300 mg/kg/day x 30 days		
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	358.8	14.45*	4.016*	7.028*
	STANDARD DEV:	28.4	2.24	0.430	1.141

SEX	DOSE GROUP	TERMINAL BDDY WT (g)	ORGAN WEIGHT (g)	ORGAN-TO-BODY WT (%)	ORGAN-TO-BRAIN WT RATIO
F	1				
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	202.5	6.56	3.247	3.374
	STANDARD DEV:	13.1	0.54	0.266	0.296

TABLE 3-continued

30 DAY RANGE-FINDING ORAL TOXICITY STUDY OF BAMP IN RATS
ORGAN WEIGHT DATA
TABLE INCLUDES:
SEX = ALL; GROUP = ALL; WEEKS = ALL
DEATH = ALL; SUBSET = ALL
LIVER

F	2				
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	214.1	6.91	3.237	3.665
	STANDARD DEV:	12.2	0.76	0.379	0.440
F	3				
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	207.0	6.71	3.244	3.453
	STANDARD DEV:	17.7	0.66	0.185	0.350
F	4		100 mg/kg/day x 30 days		
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	218.3	7.88*	3.608	4.179*
	STANDARD DEV:	16.7	1.00	0.310	0.312
F	5		300 mg/kg/day x 30 days		
	NUMBER IN GROUP:	10	10	10	10
	MEAN:	205.9	7.88*	3.832*	4.313*
	STANDARD DEV:	14.3	0.88	0.419	0.457

*significantly different from control value $p \leq 0.05$
RT - Date analyzed following rank transformation.

Conclusions

The liver of rats exposed to BAMP by oral gavage for at least 30 days showed no histologic evidence of an adverse effect at the highest dose level employed (300 mg/kg/day).

The results were compared with the comparative examples in Table I which showed the greatest efficacy and greatest PI values, viz., the compound of Comparative Example 1 (hereinafter referred to as Compound A), Comparative Example 6 (hereinafter referred to as Compound B) and Comparative Example 13 (hereinafter referred to as Compound C).

COMPARATIVE EXAMPLE 14

Compound C, i.e., N-acetyl-D, L-phenylglycine N-benzylamide was subjected to 5-day chronic treatment on anticonvulsant activity (maximal electroshock). 3 groups of 8 animals each were treated as follows. One group was given the MES ED_{50} of the test drug for 5 days; the second group was given the requisite volume of the vehicle (0.04 ml/10 g body wt.) for 4 days and a single dose (MES ED_{50}) of the test drug on day 5; and the third group was given the requisite volume of the vehicle daily for 5 days. At the time of peak effect of the candidate substance on day 5, all groups were subjected to the MES test and the number of animals protected recorded. Seizure components of the unprotected animals were timed to the nearest 10th of a second and the extensor/flexor (E/F) ratio, S.E., and p value determined. Since extensor duration decreases and flexor duration increases as a maximal seizure is attenuated, the E/F ratio provides a measure of seizure severity.

All rats subjected to the 5-day tolerance studies were maintained in their home cage for 24 hours and then subjected to the hexobarbital sleep time test (day 6). Each rat in each of the 3 groups was given 100 mg/kg of hexobarbital (i.p.) and the sleep time measured to the nearest minute. The mean sleep time and S.E. for each group were calculated. If the mean sleep time of the treated group was significantly less than that of the treated-control group, it was considered suggestive of metabolic tolerance.

Two of the three groups of animals subjected to the hexobarbital sleep time test (chronically treated and vehicle control groups) were continued on their respective original treatment regimen for two days (days 6 and 7) and 24 hours later (day 8) subjected to liver microsomal studies. The rats were decapitated and the livers perfused with 0.9% sodium chloride solution. The livers were removed, weighed, and homogenized in 0.25M sucrose. Microsomes were prepared and their drug metabolizing capabilities (microsomal protein yield; cytochrome P-450 concentration; p-nitroanisole O-demethylase and NADPH cytochrome c reductase activities; norbenzphetamine MI complex formation; and glucuronyl transferase, erythromycin demethylase, and ethylmorphine demethylase activities) measured (Arch. Biochem. Biophys. 143: 318–329, 1971).

The chronic studies in rats demonstrate that 5 daily doses of 48 mg/kg of Compound C does not affect either the anticonvulsant activity or hexobarbital sleep time. In contrast, chronic administration of Compound C induces some liver microsomal enzyme systems as indicated by the significant increases in p-nitroanisole O-demethylase, ethylmorphine demethylase, and NADPH cytochrome c reductase activities. See Table 4.

TABLE 4

ANTICONVULSANT SCREENING PROJECT TEST RESULTS
PHASE VII EVALUATION, Rats, p.o.
CMPD C
Solvent: 30% PEG (M&P, SB)
Ave. Animal Wt: 123.3 g. TPE 4 hrs, ED50 48 mg/kg
B. EFFECT OF CHRONIC ADMINISTRATION ON THE LIVER MICROSOMAL SYSTEM

Parameter	Control	Treated 7 Days
Body Weight (g)	148.8 ± 4.3	146.3 ± 3.8
Liver Weight (g)	8.36 ± 0.26	8.54 ± 0.26
Total Protein (mg)	30.0 ± 1.6	31.7 ± 1.4
Cytochrome P-450 (nmoles/mg)	0.60 ± 0.02	0.71 ± 0.06
p-nitroanisole O-demethylase (nmoles/mg/min)	0.56 ± 0.04	0.82 ± 0.12*
NADPH Cytochrome c reductase (nmoles/mg/min)	137.8 ± 9.2	160.3 ± 5.2*
Norbenzphetamine MI Complex (nmoles/mg/min)	0.013 ± 0.002	0.023 ± 0.003

TABLE 4-continued

ANTICONVULSANT SCREENING PROJECT TEST RESULTS
PHASE VII EVALUATION, Rats, p.o.
CMPD C
Solvent: 30% PEG (M&P, SB)
Ave. Animal Wt: 123.3 g. TPE 4 hrs, ED50 48 mg/kg
B. EFFECT OF CHRONIC ADMINISTRATION ON THE LIVER MICROSOMAL SYSTEM

Parameter	Control	Treated 7 Days
Glucoronyl Transferase (nmoles/mg/min)	9.10 ± 0.20	9.77 ± 0.23
Erythromycin demethylase (nmoles/mg/min)	0.55 ± 0.04	0.64 ± 0.07
Ethylmorphine demethylase (nmoles/mg/min)	5.59 ± 0.37	6.75 ± 0.37*

*Significantly different from control, $p < 0.05$

These findings suggest that the compound C has an adverse effect on the liver.

As shown by the data, Compound C has a relatively less than desirable longterm, i.e., 7-day dose, profile in inducing liver enzyme. At 48 mg/kg/day (which is its effective one-time dose in preventing MES convulsion) p.o.x7 days, the data clearly show that hepatic involvement was observed in liver enzyme induction. It should be noted that if the MES-ED_{50} dose were continued for 30 days rather than 7 days, there is a high probability that more profound changes would likely have occurred, suggesting that a safety ratio of only 1 could be anticipated in a 30-day dosing schedule.

COMPARATIVE EXAMPLE 15

Compound A, i.e., N-Acetyl-D,L-alanine-N'-benzylamide was tested for its liver toxicity in accordance with the procedure described in Comparative Example 14.

The results are as follows:

The 5-day chronic studies in rats demonstrate that 5 daily doses of 48 mg/kg does not induce tolerance to the anticonvulsant effects (MES Test) of Compound A within this period of time. This interpretation is supported by the similar effectiveness of Compound A by the MES test, the increased hexobarbital sleep time, and the unaltered liver microsomal enzyme activity. In view of the increased hexobarbital sleep time in the 5-day treated animals, it was thought important to determine the in vitro effect of Compound A on p-nitroanisole O-demethylase activity. The low inhibitory potency of Compound A (I_{50}=5000 μM) suggests that there is little interference by the compound itself on hexobarbital metabolism in the sleep test. This may indicate that the potentiation of hexobarbital sleep time is central and not peripheral.

5-day tolerance studies (MES and hexobarbital sleep time tests) and 7-day liver microsomal enzyme studies in rats, indicate that tolerance was not induced by 5 daily doses of the MES ED_{50} (48 mg/kg) of Compound A (4/8 protected in the single dose acute control group; 3/8 protected in the chronically treated group); 5-day chronic treatment increased hexobarbital sleep time from that induced by a single acute dose (31.7±1.7, 34.3±1.1, and 44.4±1.9 minutes in solvent control, acute control, and 5-day treated, respectively). There was no significant change in body weight (148.8±5.9 vs 140.0±4.6 g), liver weight (7.71±0.22 vs 7.22±0.45 g), total microsomal protein (32.3±0.56±0.04 nmoles/mg), p-nitroanisole O-demethylase activity (0.50±0.04 vs 0.62±0.07 nmoles/mg/min, NADPH cytochrome c reductase activity (95.3±11.0 vs 105.0±4.1 nmoles/mg/min) in solvent control and 7-day treated, respectively. The candidate substance (Compound A) had very little inhibitory potency (I_{50}: c.5000 μM) for in vitro p-nitroanisole demethylation.

However, there was found little, if any liver enzyme induction in the 7-day study, and the compound was advanced to a 30 day dose ranging toxicology study, as that described hereinabove.

More specifically, 50 male and 50 female Crl:CoBs® CD(SD) selected from 68 male and 68 female rats (4 weeks old) were used as test animals in the study 1. The rats were housed individually in elevated wire mesh cages with food (Purina Certified Rodent Chow® 5002) and tap water (via an automated watering system) available ad libitum. Each batch of feed utilized was analyzed by the manufacturer for concentrations of specified heavy metals, aflatoxin, chlorinated hydrocarbons, organophosphates, and specified nutrients. The tap water was routinely analyzed on a retrospective basis for specified microorganisms, pesticides, heavy metals, alkalinity, and halogens for contamination. None were present in the animal feed or water at levels sufficient to interfere with this study.

During the quarantine and study periods, the room temperature and relative humidity were recorded twice daily and ranged from 64° to 77° F. and 12 to 51%, respectively. An artificial light cycle of 12 hours light and 12 hours dark was maintained.

The rats were selected for use on the study using a computer-generated weight randomization procedure and assigned to the following groups:

	No. of Rats		Compound A Dosage Levels
Group	Male	Female	mg/kg/day
1 (Control)	10	10	0
2 (low)	10	10	30
3 (Mid-1)	10	10	100
4 (Mid-2)	10	10	300
5 (High)	10	10	1000

Following randomization, the rats were identified with an ear tag bearing a unique permanent identification number. The rats were randomly assigned to treatment groups by first eliminating the ones with extreme body weights (±2 standard deviations from the mean body weight). Body weights at initiation ranged from 188.9 to 215.4 grams for the males and 141.8 to 158.8 grams for the females.

Compound Preparation and Administration

The desired amount of carboxymethyl cellulose was weighed on an appropriate (milligram) balance, transferred to a precalibrated beaker containing two-thirds of the total value of distilled water, and stirred on a magnetic stirrer until a solution formed. Distilled water was then added to final volume and stirred to achieve a 0.5% w/v solution.

Compound A was first ground into a powder. The desired amount for each dose level as weighed on an appropriate (milligram) balance and transferred into a precalibrated beaker. A small amount (0.5 to 4ml) of 0.5% carboxymethyl cellulose was added to Compound A and mixed to form a paste. Carboxymethyl cellulose (0.5%) was added to the final volume and mixed with a Tekmar® Tissumizer® for 2 to 3 minutes then mixed with a magnetic stirrer for 2 to 3 minutes. Fresh suspensions of Compound A were prepared

daily and fresh solutions of 0.5% carboxymethyl cellulose were prepared weekly and stored refrigerated.

Each rat received Compound A at a dosage factor of 10 milliliters per kilogram of body weight via gavage between 9 a.m. and noon each day. The dosing volume for each rat was calculated and adjusted weekly by the computer from the most recently recorded individual body weight.

Compound A was administered orally.

Reserve samples of carboxymethyl cellulose (1 gram), distilled water (10 milliliters), and Compound A (1 Gram) were taken at initiation and stored at room temperature.

All rats were observed twice daily for mortality and moribundity. Clinical observations were made prior to dosing and at 1 and 4 hours after dosing. All signs were recorded as they were observed. Individual body weights were recorded at initiation of treatment, at weekly intervals, and at termination while food consumption was recorded weekly.

Sacrifice and Gross Pathology

Following 30 or 31 days of treatment, surviving rats were weighed, anesthetized, and exsanguinated under sodium pentobarbital anesthesia. Complete necropsies were performed on each rat by appropriately trained personnel using procedures approved by board-certified pathologists. Necropsy included examination of the following:

External surface

All orifices

Cranial cavity

Carcass

External surface of the brain and spinal cord (postfixation)

Nasal cavity and paranasal sinuses

Thoracic, abdominal, and pelvic cavities and their viscera

Cervical tissues and organs

All findings were recorded.

Gross Pathology

Individual gross pathology findings are as follows:

A possible compound-related effect on the kidneys was observed. Dilated pelves were noted in three males and two females in Group 5, one male each in Groups 3 and 4, and one female in Group 1. Other observations noted which appear to be incidental and not compound-related included dark areas on the lungs, liver, thymus, stomach, and cecal mucose, granular spleen, raised area on the liver, fluid-distended uterus, fluid in the cranial cavity, and a small, soft testis.

Organ Weights and Organ/Body Weight Ratios

Various organs were weighted and compared to the control, e.g., brain with stem, heart, spleen, kidney, liver, sex organs. Only the liver weights were significantly different from the control value as shown in Table 5.

TABLE 5

PATH/TOX SYSTEM OUTPUT
THIRTY-DAY DOSE RANGE FINDING STUDY OF COMPOUND A IN RATS
ORGAN TO TERMINAL BODY WEIGHT RATIO MEANS (%)
TABLE INCLUDES:
SEX = ALL; GROUP = ALL; WEEKS = ALL
DEATH = ALL; SUBSET = ALL

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
				BR - BRAIN W/STEM						
# IN GRP:	10	10	10	10	10	10	10	10	10	10
MEAN:	.588	.593	.599	.581	.571	.918	.887	.899	.934	.891
STAND DEV:	.034	.065	.037	.019	.035	.048	.043	.044	.073	.079
				HT - HEART						
# IN GRP:	10	10	10	10	10	10	10	10	10	10
MEAN:	.321	.313	.314	.328	.343	.358	.372	.345	.373	.347
STAND DEV:	.027	.021	.037	.055	.057	.029	.039	.035	.028	.033
				SP - SPLEEN						
#IN GRP:	10	10	10	10	10	10	10	10	10	10
MEAN:	.176	.172	.166	.163	.176	.200	.204	.200	.198	.189
STAND DEV:	.029	.027	.020	.013	.021	.034	.022	.021	.036	.016
				KD - KIDNEY						
# IN GRP:	10	10	10	10	10	10	10	10	10	10
MEAN:	.732	.719	.694	.695	.770	.753	.773	.768	.770	.763
STAND DEV:	.038	.043	.055	.047	.063	.063	.063	.043	.043	.054
				LI - LIVER						
# IN GRP:	10	10	10	10	10	10	10	10	10	10
MEAN:	2.846	2.849	3.059*	3.101*	3.683*	3.004	3.122	3.166	3.172	3.739*
STAND DEV:	.183	.167	.238	.147	.173	.249	.211	.147	.167	.242
				TP - TESTIS/EPIDID						
# IN GRP:	10	10	10	10	10	0	0	0	0	0

TABLE 5-continued

PATH/TOX SYSTEM OUTPUT
THIRTY-DAY DOSE RANGE FINDING STUDY OF COMPOUND A IN RATS
ORGAN TO TERMINAL BODY WEIGHT RATIO MEANS (%)
TABLE INCLUDES:
SEX = ALL; GROUP = ALL; WEEKS = ALL
DEATH = ALL; SUBSET = ALL

SEX:	MALE					FEMALE				
GROUP:	1	2	3	4	5	1	2	3	4	5
NUMBER:	10	10	10	10	10	10	10	10	10	10
MEAN:	1.251	1.265	1.219	1.212	1.202					
STAND DEV:	.171	.118	.136	.098	.099					

*Significantly different from the control value, ($p \leq .05$).

Thus, the mean liver weight was increased in the males of Groups 4, (300 mg/kg/day×30 days) and 5 (1000 mg/kg/day×30 days) in the Group 5 females. This was reflected by increases in the liver/body weight ratios. The liver/body weight ratio was also noted for the Group 3 (100 mg/kg/day×30 days) males. The only other change of note was a small increase in the mean kidney weight of the Group 5 males.

Thus, using a daily dose of 100 mg/kg as a threshold dose to a potentially hepatotoxic dose, this would give a liver safety ratio against the anti-convulsant dose of 2.1.

COMPARATIVE EXAMPLE 16

Compound C, i.e., D-(−)-α-acetamido-N-benzyl-2-furanacetylamide was evaluated for liver toxicity using the procedures described hereinabove. More specifically, various dosages such as 25 mg/kg, 100 mg/kg, 500 mg/kg of the drug was administered by oral gavage to rats for a set period of time. The rats were housed separately. The rats were periodically viewed for mortality and moribundity. At the termination of the study, the surviving rats were anesthetized, and exsanguinated under anesthesia. Complete necropsies were performed by appropriately trained personnel using procedures approved by board certified pathologists and the results were recorded.

When the D-furyl derivative of Comparative Example 6 was administered to the rat, hepatocellular necrosis was evident at 100 and 25 mg/kg in rats treated for 13 weeks.

The data respecting these compounds tested BAMP, compounds A, B and C are summarized in Table 6.

TABLE 6

	MOUSE			RAT					
	anticonvulsant dose			anticonvulsant			Liver Pathology oral, multiple doses		Safety
	Route i.p. ED_{50}(95% C.L.) mg/kg		Ratio to MES	Oral ED_{50}(95% C.L.) mg/kg		Ratio to			
	MES	Neurotox	(p.2)	MES	Neurotox	MES	Dose	Pathology Report	Ratio daily dose; MES (p.2)
Compound C D.L-phenyl	20.3 (16.8–24.5)	96.9 (79.8–118)	4.8	48.3 (3.31–68)	>1000	20.7	48 mg/kg/day × 7 days	liver enzyme induction	−1
Compound A D,L methyl	76.5 (66.6–89.0)	454 (417–501)	5.9	48.2 (32.0–71.8)	>1000	20.8	100 mg/kg/day × 30 days	liver to body wt. ratio increased male	2.1
							300 mg/kg/day × 30 days	absolute weight liver inc. - male	−6.3
Compound B D-furan	3.3 (2.8–3.9)	23.8 (17.2–30.7)	7.2	1.97 (1.07–3.3)	333 (259–411)	175	25 mg/kg/day × 30 days	hepatocellular necrosis	12.7
BAMP D-methoxy-methyl	4.46 (3.72–5.46)	26.8(25.5–28.0)	6.0	3.90 (2.58–6.20)	>500	>128	100 mg/kg/day × 30 days	liver to brain wt. ratio increased-female	25.6
							300 mg/kg day × 30 days	no adverse histologic effects	>76.9

MES - Maximal Eletrochock Seizure test
Neurotox - rotorod test determined at peak effect

As clearly, shown by the data in Table 6, the ED_{50} value in the MES test for BAMP is significantly less (significantly

more effective) than that of Compounds A and C and is of the same order of magnitude with respect to Compound B. Moreover, the PI ratio of BAMP is significantly greater than that of Compounds A and C.

However, and most importantly, BAMP had no histopathologic indications at the higher dose (300 mg/kg/day for 30 days) and exhibited a minor deviation at the lower dosage. This is in complete contrast to the liver pathology of Compounds A, C and especially B. All of the comparative examples showed significantly greater liver toxicity than BAMP. This is seen in the safety ratio daily dose of MES, shown in the last column in the table. In this table, the daily dose given for multiple consecutive days at which the first indications of liver toxicity is noted. That ratio, expressed against the oral anticonvulsant MES single dose, is a safety index for onset of liver problems upon chronic administration of drug. As shown in the table, the safety ratio for the dose to signs of liver enlargement following 30 days medication relative to an oral anti-convulsant dose was 2.1 for Compound A, but was 25.6 for BAMP. For histologic signs of liver toxicity, including, for example, hepatocellular necrosis, the safety ratio was 12.7 for Compound B. In contrast, 30 days chronic dosing with BAMP caused no adverse histologic effects at 76.9 times its anti-convulsant dose.

Thus, the toxicity of the compounds of the present invention when administered for extended periods to the animal is an important parameter. Even when an anti-convulsant has active efficacy, if it shows toxicity to the animal, it is unlikely that it will be a candidate for use in chronic dosing. Thus, in selecting an anti-convulsant it is not only important that is satisfies the three criteria outlined hereinabove (high efficiency, low neurological toxicity, high P.I.) but also the fourth criteria, low toxicity. The compounds of the present invention meet these criteria.

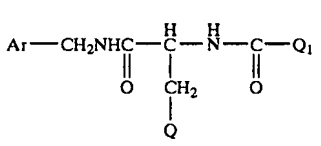
Thus, as clearly shown by the data the compounds of the present invention have low liver toxicity required of drugs to be used in chronic administration and are thus quite safe. The compounds of the present invention exhibit none or minimal effects on the liver.

Thus, the compounds of the present invention exhibit an excellent drug profile. They meet all of the four characteristics outlined heretofore, high potency, low neurological toxicity relative to its potency, high protective index and minimal liver toxicity. The compounds of the present invention are substantially non-toxic to the liver. These compounds of the present invention exhibit advantages that have not heretofore been realized. They therefore can be used in a treatment regimen requiring administration thereof over extended periods of time (chronic administration).

The above preferred embodiments and examples are given to illustrate the scope and spirit of the present invention. The embodiments and examples described herein will make apparent to those skilled in the art other embodiments and examples. These other embodiments and examples are within the contemplation of the present invention. Therefore, the present invention should be limited only by the appended claims.

What is claimed is:

1. A compound in the R configuration having the formula:



wherein

Ar is phenyl which is unsubstituted or substituted with at least one halo group;

Q is lower alkoxy, and

Q_1 is methyl.

2. The compound according to claim **1** which is substantially enantiopure.

3. The compound according to claim **1** wherein Q is lower alkoxy containing 1–3 carbon atoms.

4. The compound according to claim **3** wherein Q is methoxy.

5. The compound according to claim **1** wherein Ar is unsubstituted phenyl.

6. The compound according to claim **1** wherein halo is fluoro.

7. The compound according to claim **1** wherein Q is alkoxy containing 1–3 carbon atoms and Ar is unsubstituted phenyl.

8. The compound according to claim **1** which is (R)-N-Benzyl 2-Acetamido-3-methoxypropionamide.

9. The compound according to claim **8** which contains at least 90% (w/w) R stereoisomer.

10. A therapeutic composition comprising an anticonvulsant effective amount of a compound according to any one of claims **1–9** and a pharmaceutical carrier therefor.

11. A method of treating central nervous system disorders in an animal comprising administering to said animal in need thereof an anticonvulsant effective amount of a compound according to any one of claims **1–9**.

12. The method according to claim **11** wherein the animal is a mammal.

13. The method according to claim **12** wherein the mammal is a human.

* * * * *

Exhibit E

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5,773,475	**$850.00**	**$0.00**	**09/28/01**	**08/818,688**	**06/30/98**	**03/17/97**	**04**	**NO**	**10030**

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PATENT NUMBER	FEE AMT	SUR CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SMALL ENTITY?	ATTY DKT NUMBER
RE38,551	**$2,300.00**	**$0.00**	**11/23/05**	**10/058,634**	**06/30/98**	**03/17/97**	**08**	**NO**	**RE10030I**

Exhibit F

Exhibit F

A brief description of significant activities undertaken by the sponsor, Schwarz Biosciences, Inc. ("Schwarz") (or its predecessor in interest), during the regulatory review period for VIMPAT® (lacosamide) injection, together with applicable dates, follows below.

1. Overview

Between November 14, 2003 and September 28, 2007, Schwarz conducted two clinical studies of VIMPAT® injection to identify the appropriate infusion duration(s) for VIMPAT® as short-term replacement for oral VIMPAT® and to provide data to support the safety of that infusion duration. Schwarz also conducted at least four pharmacokinetic and pharmacodynamic studies.

Between September 28, 2007 and October 28, 2008, Schwarz responded to numerous requests for information from FDA. The dates of those responses are summarized in Section 4.

2. Key Regulatory Dates

October 15, 2003	IND 68,407 submitted to FDA
November 14, 2003	FDA notification (via telephone) that IND 68,407 is in effect
December 24, 2003	FDA confirmation (via letter) that IND 68,407 is in effect[1]
December 9, 2004	End-of-Phase II Meeting with FDA
July 19, 2006	Pre-NDA Meeting with FDA
September 6, 2006	Meeting with FDA regarding abuse liability
September 28, 2007	NDA 22-254 submitted to FDA
October 22, 2007	FDA letter acknowledging receipt of NDA
December 10, 2007	FDA letter accepting NDA for filing
July 31, 2008	FDA letter extending NDA review date until October 28, 2008
October 28, 2008	FDA approval letter of NDA 22-254

[1] Applicant notes that IND 57,939 for VIMPAT® (lacosamide) tablet went into effect on May 19, 1999. Thus, certain dates relating to that IND may be relevant should the FDA determine that the present application is entitled to that date. Applicant will supplement this Exhibit upon request should information from IND 57,939 be determined by the FDA to be relevant.

3. Summary of Phase III Clinical Studies

Start	Stop	Study
FSI 04 Mar 2004	LSO 17 Aug 2004	SP616 (multicenter, double-blind, double-dummy randomized study to investigate safety, tolerability, and pk of intravenous lacosamide as replacement for oral lacosamide in subjects with partial seizures with or without secondary generalization)
FSI 03 Feb 2005	LSO 10 May 2006	SP757 (multicenter, open-label study to investigate the safety and tolerability of intravenous lacosamide as replacement for oral lacosamide in subjects with partial seizures with or without secondary generalization)

4. NDA Amendments

Following the initial submission of the NDA on September 28, 2007, Schwarz submitted additional information to FDA on the following dates:

November 26, 2007
December 13, 2007
January 23, 2008
February 13, 2008
February 22, 2008
March 20, 2008
April 3, 2008
April 9, 2008
April 14, 2008
April 18, 2008
April 30, 2008
May 9, 2008
May 27, 2008
June 11, 2008
July 11, 2008 (2)
July 17, 2008
July 30, 2008
August 1, 2008
August 14, 2008
August 27, 2008
September 4, 2008
September 23, 2008
October 15, 2008
October 21, 2008

5. Additional Information

A more detailed description of the activities undertaken by the NDA holder, including those otherwise listed above in this Exhibit, is set forth in the IND 68,407 Submissions and NDA 22-254 Submissions tables (each table being produced across multiple pages that are independently numbered) produced on the remainder of the pages of this Exhibit.

IND 68,407 Submissions

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
15-Oct-03	0000		Initial IND	SP616	Draft protocol		
15-Oct-03	0000		Initial IND		Evaluation of the pharmacokinetic profile of SPM 927		
15-Oct-03	0000		Initial IND		Investigator brochure		
15-Oct-03	0000		Initial IND	SP658	Randomized, open-label, single-dose, three-way crossover trial to compare the pharmacokinetics of SPM 927 when given a intravenous solution or as oral tablet in 24 healthy male subjects		
15-Oct-03	0000		Initial IND	SP643	Randomized, open-label, two-way crossover trial to investigate the pharmacokinetics and bioavailability of SPM 927 in poor and extensive metabolizers (cyp 2c19)		
15-Oct-03	0000		Initial IND		Cross reference all preclinical and clinical reports from oral IND.		
03-Nov-03			Response to FDA Request for Information		Send Tom Broadbent, FDA, fax of certificate of analysis for DS, rationale for vials filled with 21.0mL, and 20 L beaker.		
04-Nov-03			Response to FDA Request for Information		Send Tom Broadbent, FDA, fax of detailed information on vial and beakers for IV formulation.		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
14-Nov-03			FDA Phone Contact		Ms. Griffis, FDA, calls with okay to proceed with IV trial SP616 and apology for comments on safety package being delayed.		
18-Nov-03	0001		Initial Safety Report	SP665		2003-00393	10344
19-Nov-03	0002	v1 p1	Information Amendment: Clinical	SP600	Open-label randomized, single dose, two-way cross-over study to evaluate the effect of food on the bioavailability of SPM 927 (harkoseride) in healthy male caucasian volunteers.		
19-Nov-03	0002	v3 p1	Information Amendment: Clinical	SP601	Open-label randomized, multiple dose, cross-over study to evaluate the pharmacokinetic effect of SPM 927 (harkoseride) on valproic acid (VPA) in 16 healthy male caucasian volunteers.		
02-Dec-03	0003		Follow-up Safety Report	SP667		2002-00244	12803/80017
03-Dec-03	0004		Follow-up Safety Report	SP655		2002-00095	10001/80037
05-Dec-03	0005		Initial Safety Report	SP667		2003-00287	10404/80291
05-Dec-03	0006		Follow-up Safety Report	SP615		2002-00044	10027/10027
08-Dec-03	0007		General Correspondence		Schwarz sends correction letter to 5-dec-2003 serial no. 0006. Incorrect version of CIOMS report was attached.		
17-Dec-03	0008		Follow-up Safety Report	SP615		2003-00248	10502

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
18-Dec-03	0009		Protocol Amendment: New Protocol	SP616	New protocol		
19-Dec-03	0010		Initial Safety Report	SP615		2003-00450	11488
23-Dec-03	0011		Follow-up Safety Report	SP667		2003-00287	10404/80291
24-Dec-03			FDA Correspondence	SP616	FDA sends IND review letter with comments and recommendations regarding clinical, phamacokinetics, development plan and protocol SP616.		
30-Dec-03	0012		Initial Safety Report	SP615		2003-00474	11503
09-Jan-04	0013		Information Amendment: CMC Data		Revised CMC information including control of excipients, control of drug product and three month stability data for one batch of solution for injection.		
13-Feb-04	0014		Protocol Amendment: Change in Protocol	SP615	Amendment 5		
13-Feb-04	0014		Information Amendment: Clinical	SP619	Open-label, randomized, single dose study to evaluate the absorption, metabolism, and excretion of [14C]-labeled SPM 927 (harkoseride) following oral and intravenous administration to 10 healthy male caucasian subjects		
13-Feb-04	0014		Protocol Amendment: Change in Protocol	SP616	Amendment 1		
13-Feb-04	0014		Response to FDA Request for Information		Schwarz responds to FDA etter 24-dec-2003 comments and recommendations.		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
18-Feb-04	0015		Initial Safety Report	SP615		2004-00049	11281
24-Feb-04	0016		Follow-up Safety Report	SP615		2003-00474	11503
10-Mar-04	0017		General Correspondence	SP640	Submit pain protocol SP640 to epilepsy INDs for information purposes only.		
18-Mar-04	0018		Protocol Amendment: New Investigator	SP616	New investigators		
01-Apr-04	0019		Initial Safety Report	SP615		2004-00129	11610
01-Apr-04	0019		Initial Safety Report	SP665		2004-00135	10175
06-Apr-04	0020		Follow-up Safety Report	SP615		2003-00248	10501
15-Apr-04	0021		Follow-up Safety Report	SP665		2004-00135	10175
19-Apr-04	0022		Protocol Amendment: New Investigator	SP616	New and Revised investigators		
03-May-04	0023		Initial Safety Report	SP615		2004-00189	10185
12-May-04	0024		Follow-up Safety Report	SP615		2004-00129	11610
19-May-04	0026		Initial Safety Report	SP615		2004-00232	11478
20-May-04	0027		Protocol Amendment: New Investigator	SP616	New investigator		
27-May-04	0028		Follow-up Safety Report	SP615		2004-00049	11281

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
02-Jun-04			7-Day Safety Report	SP615	Fax 7-day safety report to Ms. Griffis, FDA.	2004-00274	11428
02-Jun-04	0029		7-Day Safety Report	SP615		2004-00274	11428
07-Jun-04	0030		Initial Safety Report	SP615		2004-00266	10194
21-Jun-04	0031		Protocol Amendment: New Investigator	SP616	New and revised investigators		
24-Jun-04	0032		Follow-up Safety Report	SP615		2004-00266	10194
24-Jun-04	0032		Follow-up Safety Report	SP615		2004-00274	11428
28-Jun-04	0033		Initial Safety Report	SP742		2004-00326	15502/80010
28-Jun-04	0033		Initial Safety Report	SP743		2004-00321	11406/8011
28-Jun-04	0034		Annual Report		Period covering 15-OCT-2004 through 25-MAR-2004		
01-Jul-04			Initial Safety Report	SP742	Fax 7-day safety reports to FDA	2004-00356	13002/80062
01-Jul-04			7-Day Safety Report	SP743	Fax 7-day safety reports to FDA	2004-00355	12307
01-Jul-04	0035		Follow-up Safety Report	SP667		2003-00298	11910/80301
01-Jul-04	0035		Follow-up Safety Report	SP615		2004-00232	11478
01-Jul-04	0036		7-Day Safety Report	SP743		2004-00355	12307

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
01-Jul-04	0036		Initial Safety Report	SP742		2004-00356	13002/80062
13-Jul-04	0037		Follow-up Safety Report	SP743		2004-00355	12307/80040
13-Jul-04	0037		Follow-up Safety Report	SP742		2004-00326	15502/80010
13-Jul-04	0038		Initial Safety Report	SP743		2004-00366	12302/80036
14-Jul-04			7-Day Safety Report	SP743	Fax Ms. Griffis, FDA, 7-day safety report	2004-00380	15712/80094
14-Jul-04	0039		7-Day Safety Report	SP743		2004-00380	15712/80094
19-Jul-04	0040		Initial Safety Report	SP742		2004-00370	13805/80082
21-Jul-04	0041		Information Amendment: Clinical	SP588	Multiple dose tolerance study with ascending oral doses of SPM 927 (harkoseride) in healthy male caucasian volunteers		
21-Jul-04	0042		Follow-up Safety Report	SP742		2004-00356	13002/80062
04-Aug-04			7-Day Safety Report	SP742	Fax Ms. Griffis, FDA, 7-day safety report	2004-00428	14309
04-Aug-04	0043		7-Day Safety Report	SP742		2004-00428	14309
05-Aug-04	0044		Follow-up Safety Report	SP615		2004-00266	10194
05-Aug-04	0044		Follow-up Safety Report	SP743		2004-00321	11406/80110
05-Aug-04	0044		Follow-up Safety Report	SP743		2004-00380	15712/80094

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
05-Aug-04	0044		Follow-up Safety Report	SP615		2004-00232	11478
09-Aug-04			7-Day Safety Report	SP742	Fax Ms. Griffis, FDA, 7-day safety report	2004-00441	15601/80177
09-Aug-04	0045		7-Day Safety Report	SP742		2004-00441	15601/80177
10-Aug-04	0046		Information Amendment: Clinical		Revised investigator's brochure dated May 2004		
12-Aug-04			7-Day Safety Report	SP743	Fax Ms. Griffis, FDA, 7-day safety report	2004-00447	17508/80301
12-Aug-04	0047		Follow-up Safety Report	SP742		2004-00428	14309/80133
12-Aug-04	0047		Follow-up Safety Report	SP742		2004-00370	13805/80082
12-Aug-04	0048		7-Day Safety Report	SP743		2004-00447	17508/80301
16-Aug-04	0049		Initial Safety Report	SP743		2004-00443	16811/80194
23-Aug-04	0050		Follow-up Safety Report	SP743		2004-00447	17508/80301
23-Aug-04	0050		Follow-up Safety Report	SP743		2004-00443	16811/80194
23-Aug-04	0050		Follow-up Safety Report	SP743		2004-00355	12307/80040
23-Aug-04	0050		Follow-up Safety Report	SP615		2003-00323	10616/10538
24-Aug-04			7-Day Safety Report	SP742	Fax Ms. Griffis, FDA, 7-day safety report	2004-00483	15210/80059

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
24-Aug-04	0051		7-Day Safety Report	SP742		2004-00483	15210/80059
25-Aug-04	0052		Response to FDA Request for Information	SP742	Respond to FDA request for follow-up information regarding this case; requested on 10-AUG-2004.	2004-00356	13002/80062
30-Aug-04	0053		Follow-up Safety Report	SP742		2004-00370	13805/80082
30-Aug-04	0053		Follow-up Safety Report	SP742		2004-00356	13002/80062
02-Sep-04			7-Day Safety Report Fax	SP743	Fax Ms. Griffis, FDA, 7-day safety report	2004-00507	14919
02-Sep-04	0054		7-Day Safety Report	SP743		2004-00507	14919
09-Sep-04	0055		Follow-up Safety Report	SP615		2004-00274	11428
09-Sep-04	0055		Follow-up Safety Report	SP743		2004-00447	17508/80301
09-Sep-04	0055		Follow-up Safety Report	SP743		2004-00443	16811/80194
09-Sep-04	0056		Meeting Request		Schwarz requests end of phase 2 type B meeting to discuss clinical development program for the iv formulation.		
14-Sep-04			FDA Phone Contact		Ms. Griffis, FDA, calls to give end of phase 2 meeting date of 9-DEC-2004.		
14-Sep-04			FDA Correspondence		Ms. Giffis, FDA, emails date of 9-DEC-2004 for end of phase 2 meeting.		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
15-Sep-04			General Correspondence		Email Ms. Griffis, FDA, question on how the FDA will proceed with review of the CMC section.		
17-Sep-04			FDA Correspondence		Ms. Griffis, FDA, emails that once the briefing document is received she will have the chemist review it and determine if a meeting is needed.		
23-Sep-04			7-Day Safety Report	SP742	Fax Ms. Griffis, FDA, 7-day safety report	2004-00553	13308/80166
23-Sep-04	0057		7-Day Safety Report	SP742		2004-00553	13308/80166
27-Sep-04	0058		Initial Safety Report	SP742		2004-00544	15803
27-Sep-04	0058		Initial Safety Report	SP742		2004-00551	14609
29-Sep-04	0059		Follow-up Safety Report	SP742		2004-00428	14309/80133
29-Sep-04	0059		Follow-up Safety Report	SP743		2004-00507	14919
29-Sep-04	0059		Follow-up Safety Report	SP743		2004-00443	16811/80194
08-Oct-04	0060		Initial Safety Report	SP615		2004-00573	10529
13-Oct-04			7-Day Safety Report	SP615	Fax Ms. Griffis, FDA, 7-day safety report	2004-00580	10626
13-Oct-04	0061		7-Day Safety Report	SP615		2004-00580	10626
15-Oct-04			7-Day Safety Report	SP754	Fax Ms. Griffis, FDA, 7-day safety report	2004-00616	15605

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
15-Oct-04	0062		7-Day Safety Report	SP754		2004-00616	15605
19-Oct-04	0063		Follow-up Safety Report	SP754		2004-00616	15605
19-Oct-04	0063		Follow-up Safety Report	SP742		2004-00551	14609
19-Oct-04	0063		Follow-up Safety Report	SP742		2004-00553	13308/80166
19-Oct-04	0063		Follow-up Safety Report	SP742		2004-00544	15803
19-Oct-04	0063		Follow-up Safety Report	SP615		2004-00573	10529
20-Oct-04			FDA Correspondence		Ms. Griffis, FDA, emails that the chemist is reviewing the package.		
21-Oct-04			FDA Correspondence		Ms. Griffis, FDA, emails that the CMC team does not need to attend the 57,939 meeting as she hope to have CMC questions answered soon.		
25-Oct-04	0064		Initial Safety Report	SP743		2004-00614	17603/80422
26-Oct-04	0065		Meeting Package		End of phase 2 meeting package for meeting scheduled 9-DEC-2004.		
01-Nov-04	0066		Follow-up Safety Report	SP743		2004-00380	15712/80094
08-Nov-04			7-Day Safety Report	SP742	Fax Ms. Griffis, FDA, 7-day safety report	2004-00599	14004/80152
08-Nov-04	0067		7-Day Safety Report	SP742		2004-00599	14004/80152

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
10-Nov-04	0068		Initial Safety Report	SP615		2004-00665	10402
12-Nov-04	0069		Follow-up Safety Report	SP742		2004-00551	14609
12-Nov-04	0069		Follow-up Safety Report	SP742		2004-00441	15601/80177
12-Nov-04	0069		Follow-up Safety Report	SP742		2004-00326	15502/80010
29-Nov-04	0070		Follow-up Safety Report	SP742		2004-00483	15210/80059
01-Dec-04	0071		Follow-up Safety Report	SP743		2004-00614	17603/80422
01-Dec-04	0071		Follow-up Safety Report	SP742		2004-00553	13308/80166
07-Dec-04	0072		Initial Safety Report	SP743		2004-00742	17029//80430
15-Dec-04	0073		Follow-up Safety Report	SP615		2004-00665	10402
21-Dec-04			7-Day Safety Report	SP742	Fax Ms. Griffis, FDA, 7-day safety report	2004-00791	14806/80389
21-Dec-04			7-Day Safety Report	SP768	Fax Ms. Griffis, FDA, 7-day safety report	2004-00790	112104/80001
21-Dec-04	0074		7-Day Safety Report	SP768		2004-00790	112104/80001
21-Dec-04	0074		7-Day Safety Report	SP742		2004-00791	14806/80389
22-Dec-04	0075		Follow-up Safety Report	SP743		2004-00742	17029/80430
22-Dec-04	0076		Initial Safety Report	SP746		2004-00778	17514

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
22-Dec-04	0076		Initial Safety Report	SP755		2004-00785	11601/85761
28-Dec-04			7-Day Safety Report	SP755	Fax Ms. Griffis, FDA, 7-day safety report	2004-00815	106302/82234
28-Dec-04	0077		Protocol Amendment: New Protocol	SP757	New Protocol		
28-Dec-04	0078		7-Day Safety Report	SP755		2004-00815	106302/82234
03-Jan-05			FDA Correspondence		Ms. Griffis, FDA, emails that the meeting minutes are circulating at FDA for comments and lists the FDA attendees		
03-Jan-05	0079		Follow-up Safety Report	SP755		2004-00785	11601/85761
03-Jan-05	0079		Follow-up Safety Report	SP743		2004-00742	17029/80430
03-Jan-05	0079		Follow-up Safety Report	SP615		2004-00580	10626
06-Jan-05	0080		Information Amendment: CMC Data				
10-Jan-05	0081		Follow-up Safety Report	SP755		2004-00785	11601/85761
10-Jan-05	0081		Follow-up Safety Report	SP768		2004-00790	112104/80001
10-Jan-05	0081		Follow-up Safety Report	SP746		2004-00778	17514
10-Jan-05	0081		Follow-up Safety Report	SP742		2004-00599	14004/80152
13-Jan-05			7-Day Safety Report	SP755	Fax Ms. Griffis, FDA, 7-day safety report	2005-00008	122303/87995

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
13-Jan-05	0082		7-Day Safety Report	SP755		2005-00008	122303/87995
19-Jan-05	0083		SB Meeting Minutes		Schwarz submits meeting minutes and related attachements from end of phase 2 meeting with FDA 9-DEC-2004. Requests FDA send meeting minutes to Schwarz.		
20-Jan-05			7-Day Safety Report	SP742	Fax Ms. Griffis, FDA, 7-day safety report	2005-00051	14243/80369
20-Jan-05	0084		Initial Safety Report	SP755		2005-00015	110902/83890
20-Jan-05	0085		7-Day Safety Report	SP742		2005-00051	14243/80369
24-Jan-05	0086		7-Day Safety Report	SP742		2005-00059	12725/80373
24-Jan-05	0086		7-Day Safety Report	SP742		2005-00041	10911/80361
25-Jan-05			7-Day Safety Report	SP768	Fax Ms. Griffis, FDA, 7-day safety report	2005-00061	111307/80163
25-Jan-05			7-Day Safety Report	SP768	Fax Ms. Griffis, FDA, 7-day safety report	2005-00060	111305/80162
25-Jan-05	0087		7-Day Safety Report	SP768		2005-00061	111307/80163
25-Jan-05	0087		7-Day Safety Report	SP768		2005-00060	111305/80162
27-Jan-05	0088		Follow-up Safety Report	SP755		2005-00008	122303/87995
28-Jan-05			FDA Meeting Minutes		FDA emails meeting minutes from 9-DEC-2004 end of phase 2 meeting		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
28-Jan-05	0089		Initial Safety Report	SP755		2005-00049	118603/86661
01-Feb-05			7-Day Safety Report	SP755	Fax Ms. Griffis, FDA, 7-day safety report	2005-00077	10841/82989
01-Feb-05			7-Day Safety Report	SP742	Fax Ms. Griffis, FDA, 7-day safety report	2005-00088	14251/80421
01-Feb-05	0090		7-Day Safety Report	SP742		2005-00088	14251/80421
01-Feb-05	0090		7-Day Safety Report	SP755		2005-00077	10841/82989
02-Feb-05	0091		Follow-up Safety Report	SP768		2005-00060	111305/80162
02-Feb-05	0091		Follow-up Safety Report	SP768		2005-00061	111307/80163
02-Feb-05	0091		Follow-up Safety Report	SP755		2005-00015	110902/83890
02-Feb-05	0091		Follow-up Safety Report	SP755		2004-00785	116101/85761
04-Feb-05			7-Day Safety Report	SP768	Fax Ms. Griffis, FDA, 7-day safety report	2005-00096	112703/80093
04-Feb-05	0092		7-Day Safety Report	SP768		2005-00096	112703/80093
04-Feb-05	0093		Follow-up Safety Report	SP742		2005-00041	10911/80361
04-Feb-05	0093		Follow-up Safety Report	SP742		2005-00059	12725/80373
04-Feb-05	0093		Follow-up Safety Report	SP742		2005-00051	14243/80369
09-Feb-05			7-Day Safety Report	SP768	Fax Ms. Griffis, FDA, 7-day safety report	2005-00119	110403/80108

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
09-Feb-05	0094		7-Day Safety Report	SP768		2005-00119	110403/80108
09-Feb-05	0095		Follow-up Safety Report	SP755		2005-00049	118603/86661
10-Feb-05	0096		Initial Safety Report	SP768		2005-00089	112909/80024
10-Feb-05	0096		Initial Safety Report	SP754		2004-00454	15103/80069
14-Feb-05	0097		Follow-up Safety Report	SP615		2004-00580	10626
14-Feb-05	0097		Follow-up Safety Report	SP768		2005-00096	112703/80093
14-Feb-05	0097		Follow-up Safety Report	SP755		2005-00077	108401/82989
14-Feb-05	0097		Follow-up Safety Report	SP742		2004-00791	14806/80389
14-Feb-05	0097		Follow-up Safety Report	SP742		2005-00088	14251/80421
15-Feb-05	0098		Follow-up Safety Report	SP615		2004-00189	10185
17-Feb-05	0099		Protocol Amendment: New Investigator	SP757	New investigator		
24-Feb-05	0100		Initial Safety Report	SP754		2005-00160	16102/80118
24-Feb-05	0100		Initial Safety Report	SP615		2004-00732	11280
01-Mar-05			7-Day Safety Report	SP746	Fax Ms. Griffis, FDA, 7-day safety report	2005-00170	14913

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
01-Mar-05			7-Day Safety Report	SP745	Fax Ms. Griffis, FDA, 7-day safety report	2005-00168	175210
01-Mar-05	0101		7-Day Safety Report	SP745		2005-00168	175210
01-Mar-05	0101		7-Day Safety Report	SP746		2005-00170	14913
03-Mar-05	0102		Follow-up Safety Report	SP742		2005-00041	10911/80361
03-Mar-05	0102		Follow-up Safety Report	SP754		2004-00454	15103/80069
04-Mar-05	0103		7-Day Safety Report	SP755		2005-00185	116407/85873
08-Mar-05	0104		Initial Safety Report	SP756		2005-00177	15103
09-Mar-05	0105		7-Day Safety Report	SP742		2005-00193	12204/80337
11-Mar-05	0106		Initial Safety Report	SP743		2004-00444	17805/80350
14-Mar-05	0107		Follow-up Safety Report	SP754		2005-00160	16102/80118
14-Mar-05	0107		Follow-up Safety Report	SP745		2005-00168	175210
17-Mar-05	0108		Protocol Amendment: New Investigator	SP757	New investigators		
21-Mar-05	0109		Follow-up Safety Report	SP768		2005-00089	112909/80024
23-Mar-05	0110		Follow-up Safety Report	SP743		2004-00380	15712/80094

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
23-Mar-05	0110		Follow-up Safety Report	SP743		2004-00366	12302/80036
23-Mar-05	0110		Follow-up Safety Report	SP743		2004-00355	12307/80040
23-Mar-05	0110		Follow-up Safety Report	SP743		2004-00443	16811/80194
23-Mar-05	0110		Follow-up Safety Report	SP743		2004-00321	11406/80110
23-Mar-05	0110		Follow-up Safety Report	SP743		2004-00447	17508/80301
23-Mar-05	0110		Follow-up Safety Report	SP743		2004-00742	17029/80430
23-Mar-05	0110		Follow-up Safety Report	SP743		2004-00507	14919/80387
29-Mar-05	0111		Follow-up Safety Report	SP742		2005-00193	12204/80337
29-Mar-05	0111		Follow-up Safety Report	SP755		2005-00077	108401/82989
01-Apr-05	0112		Follow-up Safety Report	SP665		2002-00306	10141/10141
01-Apr-05	0112		Follow-up Safety Report	SP755		2005-00185	116407/85873
01-Apr-05	0112		Follow-up Safety Report	SP768		2005-00119	110403/80108
04-Apr-05	0113		Initial Safety Report	SP615		2005-00253	10476
12-Apr-05	0114		Follow-up Safety Report	SP746		2005-00170	14913
14-Apr-05	0115		Follow-up Safety Report	SP755		2005-00008	122303/87995

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
14-Apr-05	0115		Follow-up Safety Report	SP742		2004-00428	14309/80133
25-Apr-05	0116		Follow-up Safety Report	SP746		2005-00177	15103
25-Apr-05	0116		Follow-up Safety Report	SP746		2005-00170	14913
26-Apr-05	0117		Protocol Amendment: New Investigator	SP757	New investigators		
26-Apr-05	0118		Initial Safety Report	SP768		2005-00303	101803/80331
02-May-05	0119		Follow-up Safety Report	SP768		2005-00119	110403/80109
02-May-05	0119		Follow-up Safety Report	SP768		2005-00303	101803/80331
02-May-05	0120		7-Day Safety Report	SP755		2005-00323	106406//82279
11-May-05	0121		Initial Safety Report	SP754		2005-00341	16013/80206
11-May-05	0121		Initial Safety Report	SP830		2005-00326	110503
18-May-05	0122		Follow-up Safety Report	SP615		2005-00253	10476
20-May-05			7-Day Safety Report	SP768	Fax Ms. Griffis, FDA, 7-day safety report	2005-00375	109308/80117
20-May-05	0123		7-Day Safety Report	SP768		2005-00375	109308/80117
24-May-05	0124		Initial Safety Report	SP768		2005-00358	108702/80471

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
24-May-05	0124		Initial Safety Report	SP754		2005-00370	12804/80207
26-May-05	0125		Information Amendment: Pharmacology/Toxicology	LPT 13124/00	104-week carcinogenicity study of SPM 927 by oral administration to CD-1 mice		
26-May-05	0125		Information Amendment: Pharmacology/Toxicology	LPT 13295/00	104-week carcinogenicity study of SPM 927 by oral administration to CD-1 rats		
27-May-05			7-Day Safety Report	SP746	Fax Ms. Griffis, FDA, 7-day safety report	2005-00011	15009
27-May-05	0126		Follow-up Safety Report	SP755		2005-00077	108401/82989
27-May-05	0126		Follow-up Safety Report	SP742		2005-00193	12204/80337
27-May-05	0127		7-Day Safety Report	SP746		2005-00011	15009
01-Jun-05	0128		Protocol Amendment: Change in Protocol	SP757	Amendment 1		
02-Jun-05	0129		Information Amendment: Clinical	SP607	An open label, dose ittration trial to determine tolerability and efficacy of oral SPM 927 as adjunctive therapy in patients with partial seizures with or without secondary generalization		
03-Jun-05	0130		Initial Safety Report	SP755		2005-00405	110109/83605
03-Jun-05	0130		Initial Safety Report	SP746		2005/00409	17014
06-Jun-05	0131		7-Day Safety Report	SP768		2005-00424	101410/80256
06-Jun-05	0132		Follow-up Safety Report	SP755		2005-00323	106406/82279

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
07-Jun-05			FDA Correspondence		Ms. Griffis, FDA, provides contact information for Ms. Calder during her leave of absence		
15-Jun-05	0133		7-Day Safety Report	SP768		2005-00444	112305/80382
16-Jun-05	0134		Protocol Amendment: New Investigator	SP640	New investigator		
16-Jun-05	0134		Protocol Amendment: New Protocol	SP640	New protocol		
20-Jun-05	0135		Information Amendment: Clinical				
22-Jun-05	0136		Follow-up Safety Report	SP615		2004-00580	10626
23-Jun-05	0137		Request FDA Comment		Request biowaiver for in vivo bioequivalence study for syrup; submit core text of SP643 and SP658		
23-Jun-05	0138		Initial Safety Report	SP746		2005-00441	17415
24-Jun-05	0139		Follow-up Safety Report	SP768		2005-00375	109308/80117
24-Jun-05	0139		Follow-up Safety Report	SP755		2005-00405	110109/83605
24-Jun-05	0139		Follow-up Safety Report	SP746		2005-00409	17014
24-Jun-05	0139		Follow-up Safety Report	SP768		2005-00424	101410/80256
27-Jun-05	0140		Initial Safety Report	SP755		2005-00206	108202/82918

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
27-Jun-05	0140		Initial Safety Report	SP615		2005-00465	10477
27-Jun-05	0140		Initial Safety Report	SP756		2005-00467	16005
27-Jun-05	0141		Protocol Amendment: New Investigator	SP757	New investigators		
30-Jun-05	0142		Annual Report		period covering 26-MAR-2004 through 25-MAR-2005		
01-Jul-05	0143	v1 p1	Information Amendment: Clinical	678-02	Determination of SPM 927 and SPM 12809 in human plasma by HPLC Electrospray MS/MS after oral administration of SPM 927 and metformin to healthy male subjects (SP660)		
01-Jul-05	0143	v1 p136	Information Amendment: Clinical	679-02	Determination of SPM 927 and SPM 12809 in human urine by HPLC Electrospray MS/MS after oral administration of SPM 927 and metformin to healthy male subjects (SP660)		
01-Jul-05	0143	v2 p1	Information Amendment: Clinical	680-02	Determination of SPM 927 and SPM 12809 in human saliva by HPLC Electrospray MS/MS after oral administration of SPM 927 and metformin to healthy male subjects (SP660)		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
01-Jul-05	0143	v2 p64	Information Amendment: Clinical	031/04-05.MN	Validation of a LC/MS/MS method for the determination of metformin concentrations in human plasma and human urine samples and application of the validated assays to routine analysis of plasma and urine samples of study SP660		
06-Jul-05	0144		Follow-up Safety Report	SP768		2005-00424	101410/80256
06-Jul-05	0144		Follow-up Safety Report	SP756		2005-00444	112305/80382
06-Jul-05	0144		Follow-up Safety Report	SP768		2005-00467	16005
07-Jul-05	0145		Information Amendment: Pharmacology/Toxicology	750-03	Determination of SPM 927 and SPM 12809 in rat plasma by HPLC electrospray MS after oral administration of lacosamide to juvenile rats in a dose-range-finding study (LPT 18601/04)		
08-Jul-05	0146		Information Amendment: Clinical	SP642	Open, non-randomized, group comparison to investigate the pharmacokinetics, safety, and tolerability of 100mg SPM 927 twice daily in male and female subjects with hepatic impairment compared w/ male and female healthy subj following multiple-dose admin		
11-Jul-05			FDA Correspondence		FDA mails clarification letter to respond to a number of questions as a result of agency letter 16-MAR-2005 requesting possibly suicide related evaluation of AEs occuring in lacosamide trials		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
12-Jul-05			FDA Correspondence		FDA faxes clarification letter to respond to a number of questions as a result of agency letter 16-MAR-2005 requesting possibly suicide related evaluation of AEs occuring in lacosamide trials		
14-Jul-05	0147		Initial Safety Report	SP755		2005-00493	106305/82237
14-Jul-05	0148		Follow-up Safety Report	SP768		2005-00375	109308/80117
14-Jul-05	0148		Follow-up Safety Report	SP754		2005-00341	16013/80206
14-Jul-05	0148		Follow-up Safety Report	SP615		2004-00580	10626
18-Jul-05			7-Day Safety Report	SP830	Fax Ms. Griffis, FDA, 7-day safety report	2005-00211	108301
18-Jul-05	0149		Initial Safety Report	SP756		2005-00512	15001
18-Jul-05	0149		Initial Safety Report	SP830		2005-00492	112007
18-Jul-05	0150		7-Day Safety Report	SP830		2005-00211	108301
20-Jul-05	0151		Protocol Amendment: New Investigator	SP757	Revised investigator		
20-Jul-05	0152		Follow-up Safety Report	SP830		2005-00492	112007
21-Jul-05	0153		Follow-up Safety Report	SP755		2005-00493	106305/82237
21-Jul-05	0153		Follow-up Safety Report	SP768		2005-00444	112305/80382

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
21-Jul-05	0153		Follow-up Safety Report	SP746		2005-00441	17415
25-Jul-05	0154		7-Day Safety Report	SP768		2005-00545	108808/80185
27-Jul-05	0155		Information Amendment: Clinical	SP586	A phase II, multicenter, ascending dose assessment of the safety, tolerability, compatibility, efficacy, and pharmacokinetics of harkoseride (ADD 234037) as adjunctive therapy in patients with partial seizures		
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00551	14609/80056
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00553	13308/80166
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00599	14004/80152
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00791	14806/80389
28-Jul-05	0156		Follow-up Safety Report	SP742		2005-00041	10911/80361
28-Jul-05	0156		Follow-up Safety Report	SP742		2005-00051	14243/80369
28-Jul-05	0156		Follow-up Safety Report	SP742		2005-00059	12725/80373
28-Jul-05	0156		Follow-up Safety Report	SP742		2005-00193	12204/80337
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00544	15803/80047
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00326	15502/80010

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
28-Jul-05	0156		Follow-up Safety Report	SP742		2005-00088	14251/80421
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00441	15601/80177
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00428	14309/80133
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00370	13805/80082
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00356	13002/80062
28-Jul-05	0156		Follow-up Safety Report	SP742		2004-00483	15210/80059
28-Jul-05	0157		Follow-up Safety Report	SP756		2005-00512	15001
29-Jul-05	0158		7-Day Safety Report	SP768		2005-00556	106313/80468
29-Jul-05	0158		7-Day Safety Report	SP768		2005-00552	102704
29-Jul-05	0159		Initial Safety Report	SP768		2005-00544	114721/80494
29-Jul-05	0159		Initial Safety Report	SP768		2005-00533	103902
05-Aug-05	0160		Follow-up Safety Report	SP768		2005-00545	108808/80185
05-Aug-05	0160		Follow-up Safety Report	SP768		2005-00556	106313/80468
05-Aug-05	0160		Follow-up Safety Report	SP830		2005-00211	108301

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
08-Aug-05	0161		Information Amendment: CMC Data		Submit revised CMC information for drug substance and drug product with reference report PhTox 2678		
10-Aug-05	0162		Initial Safety Report	SP746		2005-00503	13706
10-Aug-05	0163		Information Amendment: Pharmacology/Toxicology	LPT 18772/05	Determination of SPM 927, desmethyl-SPM 927 and desacetyl-SPM 927 concentrations in mouse plasma		
10-Aug-05	0163		Information Amendment: Pharmacology/Toxicology	LPT 18447/04	Single dose pharmacokinetics of SPM 927 in CD®-1 mice		
10-Aug-05	0163		Information Amendment: Pharmacology/Toxicology	0699/025	(14C)-SPM 927: Metabolism in hepatocytes isolated from mouse, rat, rabbit, dog and man		
10-Aug-05	0163		Information Amendment: Pharmacology/Toxicology	688	Investigation of the metabolism of SPM 927 in different in vitro models		
10-Aug-05	0163		Information Amendment: Pharmacology/Toxicology	668	Evaluation of the in vivo metabolism of SPM 927 to SPM 12809 in mice, rats and dogs following repeated oral administration of SPM 927		
10-Aug-05	0163		Information Amendment: Pharmacology/Toxicology	0699/023	(14C)-SPM 927: A study of absorption, metabolism and excretion following single and multiple oral administration to the rat		
10-Aug-05	0163		Information Amendment: Pharmacology/Toxicology	728	Assessment of the systemic exposure to SPM 927, its desmethyl and its desacetyl metabolite in a single dose pharmacokinetic study of SPM 927 in male mice (188447/04, LPT)		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
10-Aug-05	0163		Information Amendment: Pharmacology/Toxicology	750-03	Determination of SPM 927 and SPM 12809 in rat plasma by HPLC-Electrospray MS after oral administration of lacosamide to juvenile rats in a dose-range-finding study (LPT 18601/04)		
15-Aug-05	0164		Information Amendment: Clinical	606-03	Re-validation of a solid-phase radioimmunoassay for determination of digoxin in human serum		
15-Aug-05	0164		Information Amendment: Clinical	682-03	Determination of SPM 927 in human plasma by HPLC Electrospray MS/MS after oral administration of SPM 927 (SP690)		
15-Aug-05	0164		Information Amendment: Clinical	651	Transport of SPM 927 across Caco-2 monolayer-Investigation of P-glycoprotein involvement		
15-Aug-05	0164		Information Amendment: Clinical	607-03	Re-validation of a solid-phase radioimmunoassay for determination of digoxin in human urine		
15-Aug-05	0165		7-Day Safety Report	SP745		2005-00597	111308
17-Aug-05	0166		Follow-up Safety Report	SP768		2005-00545	108808/80185
17-Aug-05	0166		Follow-up Safety Report	SP746		2005-00441	17415
17-Aug-05	0166		Follow-up Safety Report	SP768		2005-00556	106313/80468
19-Aug-05	0167		Follow-up Safety Report	SP830		2005-00211	108301
22-Aug-05	0168		Initial Safety Report	SP615		2004-00543	10628

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
24-Aug-05	0169		Initial Safety Report	SP745		2005-00527	170412
24-Aug-05	0169		Initial Safety Report	SP755		2005-00602	124609/88827
24-Aug-05	0169		Initial Safety Report	SP830		2005-00619	105619
25-Aug-05	0170		7-Day Safety Report	SP745		2005-00626	172706
26-Aug-05	0171		Follow-up Safety Report	SP768		2005-00552	102704
29-Aug-05	0172		7-Day Safety Report	SP768		2005-00634	104610/80545
01-Sep-05	0173		Follow-up Safety Report	SP830		2005-00619	105619
01-Sep-05	0173		Follow-up Safety Report	SP745		2005-00626	172706
01-Sep-05	0174		Initial Safety Report	SP756		2005-00635	11501
01-Sep-05	0174		Initial Safety Report	SP745		2005-00631	111607
08-Sep-05	0175		Initial Safety Report	SP640		2005-00636	82043
08-Sep-05	0175		Initial Safety Report	SP768		2005-00643	109138
08-Sep-05	0176		Follow-up Safety Report	SP746		2005-00503	13706
08-Sep-05	0176		Follow-up Safety Report	SP745		2005-00631	111607
08-Sep-05	0176		Follow-up Safety Report	SP755		2005-00323	106406/82279

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
08-Sep-05	0176		Follow-up Safety Report	SP745		2005-00626	172706
13-Sep-05	0177		7-Day Safety Report	SP863		2005-00662	80011/80011
13-Sep-05	0178		Initial Safety Report	SP756		2005-00649	12603
19-Sep-05	0179		Follow-up Safety Report	SP756		2005-00635	11501
19-Sep-05	0179		Follow-up Safety Report	SP830		2005-00619	105619
19-Sep-05	0179		Follow-up Safety Report	SP768		2005-00634	104610/80545
19-Sep-05	0179		Follow-up Safety Report	SP755		2005-00206	108202/82918
20-Sep-05	0180		Protocol Amendment: New Investigator	SP757	New and revised investigators		
20-Sep-05	0181		Information Amendment: Clinical	SP645	Randomized, open-label, single-dose, 2-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in healthy male subjects		
26-Sep-05	0182		Follow-up Safety Report	SP768		2005-00544	114721/80494
26-Sep-05	0182		Follow-up Safety Report	SP768		2005-00643	109138
26-Sep-05	0182		Follow-up Safety Report	SP768		2005-00358	108702/80471
29-Sep-05	0183		Initial Safety Report	SP774		2005-00648	104109

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
03-Oct-05	0184		Follow-up Safety Report	SP768		2005-00552	102704
03-Oct-05	0184		Follow-up Safety Report	SP756		2005-00649	12603
03-Oct-05	0184		Follow-up Safety Report	SP756		2005-00467	16005
11-Oct-05	0185		Follow-up Safety Report	SP745		2005-00527	170412
11-Oct-05	0185		Follow-up Safety Report	SP746		2005-00503	13706
11-Oct-05	0185		Follow-up Safety Report	SP755		2005-00602	124609/88827
11-Oct-05	0185		Follow-up Safety Report	SP756		2005-00635	11501
11-Oct-05	0185		Follow-up Safety Report	SP830		2005-00492	112007
13-Oct-05	0186		Initial Safety Report	SP830		2005-00645	111205
20-Oct-05	0187		Protocol Amendment: New Investigator	SP757	New and revised investigators		
26-Oct-05	0188		Follow-up Safety Report	SP830		2005-00492	112007
26-Oct-05	0188		Follow-up Safety Report	SP755		2005-00206	108202/82918
28-Oct-05	0189		7-Day Safety Report	SP768		2005-00744	108217/80452
01-Nov-05	0190		Follow-up Safety Report	SP755		2005-00323	106406/82279

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
03-Nov-05	0191		Initial Safety Report	SP615		2005-00738	11614
08-Nov-05	0192		Initial Safety Report	SP768		2005-00750	104214
08-Nov-05	0192		Initial Safety Report	SP615		2003-00367	11776
08-Nov-05	0193		Follow-up Safety Report	SP830		2005-00645	111205
10-Nov-05	0194		General Correspondence		Notify FDA of change in address and fax number		
16-Nov-05	0195		Follow-up Safety Report	SP745		2005-00597	111308
16-Nov-05	0195		Follow-up Safety Report	SP830		2005-00492	112007
22-Nov-05	0196		Initial Safety Report	SP754		2005-00775	12512/80299
30-Nov-05	0197		Information Amendment: Clinical	SP690	An open-label follow-on trial to assess the long-term safety and efficacy of oral SPM 927 in subjects with postherpetic neuralgia (PHN)		
30-Nov-05	0197		Information Amendment: Clinical	SP611	An open-label trial to assess the efficacy and safety of ascending doses of SPM 927 in subjects with chronic refractory neuropathic pain		
02-Dec-05	0198		General Correspondence		Request finalized list of FDA attendees and anticipated date of preliminary response to questions submitted in pre-NDA meeting package (Serial No. 0325); submit list of Schwarz attendees		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
05-Dec-05	0199		Follow-up Safety Report	SP768		2005-00096	112703/80093
07-Dec-05	0200		Initial Safety Report	SP774		2005-00803	110505/83749
08-Dec-05	0201		Follow-up Safety Report	SP863		2005-00662	80011/80011
13-Dec-05	0202		Response to FDA Request for Information		Submit information requested by Dr. Broadbent, FDA, for verification that both the masking agent and the strawberry flavoring are Generally Recognized as Safe (GRAS)		
14-Dec-05	0203		Follow-up Safety Report	SP615		2005-00465	10477
14-Dec-05	0203		Follow-up Safety Report	SP768		2005-00552	102704
15-Dec-05	0204		Initial Safety Report	SP830		2005-00821	110604
19-Dec-05	0205		Follow-up Safety Report	SP768		2005-00060	111305/80162
19-Dec-05	0205		Follow-up Safety Report	SP615		2005-00253	10476
20-Dec-05	0206		Initial Safety Report	SP745		2005-00827	108112
21-Dec-05	0207		Follow-up Safety Report	SP774		2005-00803	110505/83749
21-Dec-05	0208		Protocol Amendment: New Investigator	SP757	New investigator		
27-Dec-05	0209		7-Day Safety Report	SP830		2005-00843	115201

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
03-Jan-06	0210		Initial Safety Report	SP774		2005-00834	122105
03-Jan-06	0210		Initial Safety Report	SP745		2005-00848	109209
09-Jan-06	0211		Follow-up Safety Report	SP830		2005-00821	110604
09-Jan-06	0212		Request FDA Comment	754, SP755, SPE	Submit proposed statistical analysis plan for protocol SP754 which may also apply to all double-blind trials in support of the treatment of epilepsy		
09-Jan-06	0213	v1	Information Amendment: Clinical	SP616	A mutlicenter, double-blind, double-dummy, randomized trial to investigate the safety, tolerability and pharmacokinetics of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization		
09-Jan-06	0213	v2	Information Amendment: Clinical	SP661	Randomized, double-blind, placebo-controlled, parallel-group, Phase 1 trial to evaluate the pharmacokinetics, safety, and tolerability following multiple-dose oral treatment of 200mg SPM 927 in healthy male White, Black, and Asian subjects		
09-Jan-06	0213	v2 p249	Information Amendment: Clinical	SP665	An open-label follow-on trial to assess the long-term safety and efficacy of oral SPM 927 in subjects with diabetic neuropathy		
13-Jan-06	0214		7-Day Safety Report	SP746		2005-00400	16304
16-Jan-06	0215		Follow-up Safety Report	SP640		2005-00636	82043

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
16-Jan-06	0215		Follow-up Safety Report	SP745		2005-00848	109209
16-Jan-06	0215		Follow-up Safety Report	SP745		2005-00827	108112
17-Jan-06			7-Day Safety Report Fax	SP745		2006-00017	104902
17-Jan-06			General Correspondence	SP768	Email Ms. Calder, Ms. Griffis, and Ms. Malandro, FDA, notification that Schwarz will be submitting safety information		
17-Jan-06	0216		General Correspondence	SP768	Submit safety update		
17-Jan-06	0217		7-Day Safety Report	SP745		2005-00017	104902
18-Jan-06	0218		7-Day Safety Report	SP745		2006-00019	104910
20-Jan-06			General Correspondence	SP768	Email Ms. Malandro and Ms. Calder, FDA, outlier analysis for SP768 submitted 20-JAN-2006		
20-Jan-06			FDA Correspondence	SP768	Ms. Calder, FDA, confirms receipt of email containing outlier analysis for SP768		
20-Jan-06	0219		7-Day Safety Report	SP615		2005-00031	11522
20-Jan-06	0220		Protocol Amendment: New Investigator	SP767	New and revised investigators		
20-Jan-06	0221		General Correspondence	SP768	Submit outlier analysis of SP768		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
23-Jan-06			FDA Correspondence	754, SP755, SP6	Ms. Calder, FDA, emails comment from statistical team regarding proposed statistical analysis plan submitted 9-JAN-2006		
23-Jan-06	0222		General Correspondence	SP768	Submit IDMC data for 24-JAN-2006 teleconference (rescheduled to 27-JAN-2006 at 1:30pm)		
24-Jan-06	0223		Follow-up Safety Report	SP754		2005-00370	12804/80207
24-Jan-06	0223		Follow-up Safety Report	SP774		2005-00834	122105
01-Feb-06	0224		Response to FDA Request for Information	, SP746, SP830,	Submit minutes from IDMC closed session on 31-JAN-2006 and report how Schwarz is responding to IDMC's conclusions		
02-Feb-06			FDA Correspondence		Ms. Calder, FDA, emails that the Division may want to meet in the future but the medical team is still reviewing information submitted 1-FEB-2006		
02-Feb-06			General Correspondence		Email Ms. Calder, FDA, to ask if Division of Neurology Products is considering meeting over information provided 1-FEB-2006		
03-Feb-06			FDA Phone Contact		Ms. Calder, FDA, calls to notify of a 6-FEB-2006 teleconference from 3:00-4:00pm to discuss safety information for lacosamide including the data submitted 17-JAN-2006 and 1-FEB-2006		
06-Feb-06			SB Meeting Minutes		SB draft meeting minutes from 06-FEB-2006 teleconference		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
06-Feb-06			General Correspondence		Email Ms. Calder, FDA, to confirm 6-FEB-2006 teleconference and confirm conference call number and conference code		
07-Feb-06	0225		Follow-up Safety Report	SP745		2005-00631	111607
07-Feb-06	0225		Follow-up Safety Report	SP774		2005-00834	122105
08-Feb-06			FDA Correspondence		Ms. Calder, FDA, emails report of delayed email		
10-Feb-06	0226		Information Amendment: Clinical	SP598, SP660			
10-Feb-06	0227		Initial Safety Report	SP774		2006-00074	2006-00074
10-Feb-06	0227		Initial Safety Report	SP746		2006-00056	14801
16-Feb-06	0228		Follow-up Safety Report	SP746		2005-00400	16304
16-Feb-06	0228		Follow-up Safety Report	SP774		2005-00834	122105
16-Feb-06	0228		Follow-up Safety Report	SP745		2006-00019	104910
17-Feb-06	0229		Request FDA Comment		Submit revised Informed Consent Form for review		
21-Feb-06	0230		Protocol Amendment: New Investigator	SP757	New and revised investigators		
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00556	106313/80468

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00750	104214/80312
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00744	108217/80452
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00375	109308/80117
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00089	112909/80024
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00424	101410/80256
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00119	110403/80108
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00545	108808/80185
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00533	103902/80631
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00544	114721/80494
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00096	112703/80093
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00444	112305/80382
23-Feb-06	0231		Follow-up Safety Report	SP768		2004-00790	112104/80001
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00358	108702/80471
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00061	111307/80163
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00552	102704/80359

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00634	104610/80545
23-Feb-06	0231		Follow-up Safety Report	SP768		2005-00643	109138/80573
27-Feb-06	0232		7-Day Safety Report	SP830		2005-00644	105616
28-Feb-06	0233		7-Day Safety Report	SP745		2006-00114	106316
01-Mar-06	0234		Follow-up Safety Report	SP774		2006-00074	110405
01-Mar-06	0234		Follow-up Safety Report	SP774		2005-00803	110505/83749
01-Mar-06	0234		Follow-up Safety Report	SP745		2005-00597	111308
03-Mar-06	0235		General Correspondence		Request FDA review and comment on revised IB and ICF		
07-Mar-06			General Correspondence		Email Ms. Calder, FDA, about status of review of the IB and ICF for lacosamide		
08-Mar-06			FDA Correspondence		Ms. Calder, FDA, emails that she did not receive electronic copy of 03-MAR-2006 IB and ICF submission		
08-Mar-06			General Correspondence		Email Ms. Calder, FDA, first half of 03-MAR-2006 IB and ICF submission		
08-Mar-06			FDA Correspondence		Ms. Calder, FDA, emails successful receipt of electronic copy of 03-MAR-2006 IB and ICF submission		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
08-Mar-06			General Correspondence		CC Ms. Calder email copy of 03-MAR-2006 IB and ICF submission		
08-Mar-06			FDA Correspondence		Ms. Calder, FDA, emails that the Division has not yet seen 03-MAR-2006 IB and ICF submission		
08-Mar-06			General Correspondence		Email Ms. Calder, FDA, submission details for 03-MAR-2006 IB and ICF submission		
08-Mar-06			General Correspondence		Email Ms. Calder, FDA, second half of 03-MAR-2006 IB and ICF submission		
15-Mar-06	0236		Initial Safety Report	SP830		2006-00129	115104
15-Mar-06	0237		Follow-up Safety Report	SP774		2005-00803	110505/83749
15-Mar-06	0237		Follow-up Safety Report	SP746		2006-00056	14801
20-Mar-06	0238		Protocol Amendment: New Investigator	SP757	New investigators		
21-Mar-06	0239		Follow-up Safety Report	SP830		2005-00644	105616
29-Mar-06	0240		Information Amendment: Pharmacology/Toxicology	LPT 78604/02	6-Week subchronic toxicity study of SPM 927 by oral administration to juvenile CD® rats - age at start of administration: 7 days		
31-Mar-06			7-Day Safety Report Fax		Fax 31-Mar-2006 7-day safety report to Division		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
31-Mar-06	0241		7-Day Safety Report	SP757		2006-00158	170106
05-Apr-06	0242		Follow-up Safety Report	SP755		2005-00602	124609/88827
05-Apr-06	0242		Follow-up Safety Report	SP755		2005-00405	110109/83605
05-Apr-06	0242		Follow-up Safety Report	SP755		2005-00323	106406/82273
05-Apr-06	0242		Follow-up Safety Report	SP755		2005-00206	108202/82918
05-Apr-06	0242		Follow-up Safety Report	SP755		2005-00077	108401/82989
05-Apr-06	0242		Follow-up Safety Report	SP755		2005-00008	122303/87995
05-Apr-06	0242		Follow-up Safety Report	SP755		2004-00785	11601/85761
06-Apr-06	0243		7-Day Safety Report	SP757		2006-00166	170111
06-Apr-06	0244		Initial Safety Report	SP774		2006-00161	108404/8292
13-Apr-06	0245		Initial Safety Report	SP830		2006-00163	101109
14-Apr-06	0246		Meeting Request		Request Type B Pre-NDA meeting with Division of Neurology Products		
20-Apr-06	0247		Protocol Amendment: New Investigator	SP757	New investigators		
20-Apr-06	0248		Follow-up Safety Report	SP745		2006-00114	106316

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
20-Apr-06	0248		Follow-up Safety Report	SP757		2006-00158	170106
20-Apr-06	0248		Follow-up Safety Report	SP757		2006-00166	170111
21-Apr-06	0249		General Correspondence		Submit cardiovascular analysis, as requested in 6-FEB-2006 teleconference with the division		
24-Apr-06			FDA Correspondence	SP757	Ms. Calder, FDA, emails to report subject number for adverse event report referenced in same-day email	2006-00158	170106
24-Apr-06			FDA Correspondence	SP757	Ms. Calder, FDA, emails questions about adverse event report and asks that Schwarz examine possible causality to medication and adequacy of cardiac monitoring during infusion	2006-00158	170106
25-Apr-06	0250		General Correspondence	40724/1	Submit rationale and draft protocols for juvenile dog studies for FDA review and comment		
25-Apr-06	0250		General Correspondence	40724/2	Submit rationale and draft protocols for juvenile dog studies for FDA review and comment		
26-Apr-06	0251		Initial Safety Report	SP774		2006-00066	124406
27-Apr-06	0252		Initial Safety Report	SP745		2005-00598	172207
27-Apr-06	0253		Follow-up Safety Report	SP774		2006-00161	108404/8292
27-Apr-06	0253		Follow-up Safety Report	SP830		2006-00163	101109

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
28-Apr-06			General Correspondence	SP757	Email Ms. Calder, FDA, preliminary response to 24-APRIL-2006 email requesting additional safety information	2006-00158	170106
01-May-06	0254		General Correspondence	SP757	Submit requested safety information	2006-00158	170106
03-May-06			FDA Correspondence		Ms. Calder, FDA, emails additional request for suicidality data		
03-May-06	0255		Initial Safety Report	SP756		2006-00186	12202
05-May-06	0256		Information Amendment: Clinical	SP641	Open, non-randomized, sequential group comparison to investigate the pharmacokinetics, safety, and tolerability of 100mg SPM 927 in m&f subj. with renal impairment incl. subj. requiring dialysis compared with m&f healthy subj. following single-dose admin.		
11-May-06	0257		General Correspondence		Submit narratives for cardiovascular analysis		
12-May-06			General Correspondence		Email Ms. Calder, FDA, to request status of the review of draft protocols submitted 25-APR-2006		
15-May-06			FDA Correspondence		Ms. Calder, FDA, emails that toxicology reviewer will not review 25-APR-2006 draft protocols for a few weeks		
15-May-06			General Correspondence		Email Ms. Calder, FDA, to ask if a toxicologist will be reviewing 25-APR-2006 draft protocols		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
15-May-06			FDA Correspondence		Ms. Calder, FDA, emails that the 25-APR-2006 draft protocols have not been reviewed yet but would be within the next week		
15-May-06			General Correspondence		Email Ms. Calder, FDA, to ask about status of draft toxicology studies		
15-May-06			FDA Correspondence		Ms. Calder, FDA, emails that the reviewer of IB hopes to have comments within the week		
15-May-06			General Correspondence		Email Ms. Calder, FDA, thanks for information on review timeline for 25-APR-2006 draft toxicology protocol submission		
18-May-06	0258		Initial Safety Report	SP774		2006-00032	110406
18-May-06	0258		Initial Safety Report	SP754		2006-00209	14312/80405
19-May-06	0259		Protocol Amendment: New Investigator	SP757	New and revised investigators		
22-May-06	0260		Follow-up Safety Report	SP754		2005-00775	12512/80299
22-May-06	0260		Follow-up Safety Report	SP830		2006-00129	115104
22-May-06	0260		Follow-up Safety Report	SP830		2005-00644	105616
22-May-06	0260		Follow-up Safety Report	SP745		2005-00598	172207

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
26-May-06	0261		Information Amendment: Clinical	SP743	A multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 400mg/day and 600mg/day SPM 927 in subjects with painful distal diabetic neuropathy		
26-May-06	0261		Information Amendment: Clinical	SP742	A multi-center, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 200, 400, and 600mg/day SPM 927 in subjects with painful distal neuropathy		
30-May-06	0262		Protocol Amendment: Change in Protocol	SP756	Amendment 2		
30-May-06	0262		Protocol Amendment: Change in Protocol	SP754	Amendment 2		
30-May-06	0262		Protocol Amendment: Change in Protocol	SP615	Amendment 8		
01-Jun-06	0263		Follow-up Safety Report	SP774		2006-00032	110406
01-Jun-06	0263		Follow-up Safety Report	SP830		2006-00129	115104
02-Jun-06	0264		General Correspondence	SP755	Schwarz submits additional information requested by Calder, FDA, on 24-Apr-2006. Send revised narrative, cardiology consult reports and ECG reports	2006-00158	170106
16-Jun-06	0265		Meeting Package		Submit meeting package for 19-JUL-2006 Pre-NDA Meeting		
23-Jun-06	0266		Annual Report		Period covering March 26, 2005 through March 25, 2006		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
12-Jul-06	0267		Follow-up Safety Report	SP830		2006-00129	115104
18-Jul-06	0268		7-Day Safety Report	SP745		2006-00284	172723
18-Jul-06	0268		7-Day Safety Report	SP745		2006-00283	172719
20-Jul-06	0269		Protocol Amendment: New Investigator	SP767	Revised investigators		
25-Jul-06	0270		7-Day Safety Report	SP745		2006-00289	108305
31-Jul-06	0271		SB Meeting Minutes		Submit Pre-NDA Meeting Minutes from meeting held 19-JULY-2006		
02-Aug-06			General Correspondence		Mail to Dr. Levin, FDA, Type C meeting request with DNP, DAARP, and Office of Information Management to reach consesnuse with regard to technical aspects of filing lacosamide NDA		
02-Aug-06	0272		General Correspondence		Submit Type C meeting request with DNP, DAARP, and Office of Information Management to reach consesnuse with regard to technical aspects of filing lacosamide NDA		
07-Aug-06	0273		Initial Safety Report	SP756		2006-00295	18906
07-Aug-06	0273		Initial Safety Report	SP830		2006-00293	10118
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	A27033	SPM 927: Toxicity to activated sludge in a respiration inhibition test		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	A22184	SPM 927: Toxicity to scenedesmus subspicatus in a 72-hour algal growth inhibition test		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	A22206	Adsorption/desorption of [14C]-SPM 927 on soils		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	F104017	Assessment of SPM 927 in the SOD1 transgenic mouse model of ALS		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	A22173	SPM 927: Ready biodegradability in a CO2 evolution (modified Sturm) test		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	F9696	Evaluation of SPM 927 and SPM 14221 in an animal model of fibromyalgia		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	RS211	Assessment of the dependence potential of SPM 927 in rats and dogs after chronic administration and abrupt withdrawal		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	F9664	Effects of SPM 927 (harkoseride) on the development of amygdala kindling in rats		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	03.488/5	Evaluation of lacosamide, lamotrigine, levetiracetam, pregabalin, amitryptiline and venlafaxine in a model of neuropathic pain (Chung) in the rat (i.p. administration)		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	10263	In vitro pharmacology – receptor binding assay with SPM 927 and SPM 12809		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	05.122/6	Evaluation of SPM 927 in the conditioned place preference test in the rat		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	AA24877	Effects of SPM 927 (0.3, 1 and 3 mg/kg) on harmaline-induced tremors in rats		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	E-006-05-04	Electrophysiological effects of SPM 12809 on the current mediated by the SCN5A-sodium channel stably expressed in CHO-K1 cells		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	732	Determination of the cytochrome P450 induction potential of lacosamide in human hepatocytes		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	LPT 18601/04	6-week dose-range-finding study for a 6-week subchronic toxicity study of SPM 927 by oral administration to juvenile CD® rats – age at start of administration: 7 days		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	LPT 18602/04	6-week subchronic toxicity study of SPM 927 by oral administration to juvenile CD® rats – age at start of administration: 7 days		
10-Aug-06	0274		Information Amendment: Pharmacology/Toxicology	NRO 217.27.275.	Neuroprotective effect of SPM 927 on traumatic brain injury in rat		
10-Aug-06	0275		Follow-up Safety Report	SP745		2005-00597	111308
16-Aug-06	0276		Follow-up Safety Report	SP774		2006-00161	108406/8292
21-Aug-06	0277		Protocol Amendment: New Investigator	SP757	Revised investigators		
22-Aug-06	0278		7-Day Safety Report	SP830		2006-00278	112204

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
24-Aug-06	0279		Follow-up Safety Report	SP745		2006-00289	108305
24-Aug-06	0279		Follow-up Safety Report	SP756		2006-00295	18906
25-Aug-06	0280		Information Amendment: Clinical	SP658	Randomized, open-label, single-dose, 3-way crossover trial to compare the pharmacokinetics of SPM 927 when given as intravenous solution or as oral tablet in 24 healthy male subjects		
25-Aug-06	0280		Information Amendment: Clinical	SP863	Open-label multiple-dose trial to evaluate the pharmacokinetic effect of lacosamide on omeprazole and vice versa in healthy male White subjects		
25-Aug-06	0280		Information Amendment: Clinical	SP657	Randomized, open, 2-period crossover trial to show bioequivalence following single oral dosing of a tablet and of a liquid of 200mg SPM 927 each in healthy subjects		
25-Aug-06	0280		Information Amendment: Clinical	SP644	Double-blind, placebo-controlled, randomized crossover Phase I trial to investigate a possible influence of SPM 927 on the steady state pharmacokinetics, pharmacodynamics, safety and tolerability of digoxin in healthy male Caucasian subjects		
25-Aug-06	0280		Information Amendment: Clinical	SP643	Randomized, open-label, two-way crossover trial to investigate the pharmacokinetics and bioavailability of SPM 927 in poor and extensive metabolizers (CYP 2C19)		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
25-Aug-06	0280		Information Amendment: Clinical	SP599	A study of the potential pharmacodynamic and pharmacokinetic interaction of SPM 927 (harkoseride) with Microgyn® in healthy female subjects		
28-Aug-06	0281		Request FDA Comment	SP903	Request comment on abuse liability plan		
01-Sep-06	0282		7-Day Safety Report	SP745		2006-00350	101802
01-Sep-06	0282		7-Day Safety Report	SP745		2006-00357	175702
01-Sep-06	0283		Information Amendment: Clinical		Submit Investigator's Brochure dated 29-AUG-2006		
06-Sep-06			SB Meeting Minutes		Schwarz internal summary of 06-OCT-2006 meeting with the FDA to discuss lacosamide electronic submission issues		
07-Sep-06	0284		Follow-up Safety Report	SP774		2006-00161	108406/8292
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	Marzin-Lille	Expert report on the mutagenicity of SPM 927		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	LPT 17962/04	28-Day immunotoxicological study of SPM 927 by repeated oral administration to CD-1 mice – plaque forming colony (PFC) test		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	6842-103	Rising dose tolerance oral (capsule) toxicity study of ADD 234037 in dogs		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	LPT 17964/04	Acute toxicity study of SPM 927 by single oral administration to CD rats		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	Olney	Evaluation of the potential of SPM 927 to induce acute neurotoxic changes in the adult rat brain		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	S03311	An efficacy study of SPM 927 in a rat mammary tumor-induced bone pain model		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	SCHW 002	Evaluation of SPM 927 in an animal model for anxiety: stress-induced hyperthermia		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	00704	Therapeutic effect of SPM 927 in painful osteoarthritis in the rat		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	00649	Effect of SPM 927 in ddC-induced painful neuropathy in the rat		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	00580	Therapeutic effect of test compounds in painful diabetic neuropathy in the rat		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	00575	Effect of SPM 927 in vincristine-induced painful neuropathy in the rat		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	507/511	Effect of SPM 927 in two animal models of anxiety		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	505	Effect of SPM 927 in an animal model for mania		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	AA20234	Effects of SPM 927 on harmaline-induced tremors in rats		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	04.064/3	Evaluation of SPM 927 in a model of visceral pain in the rat		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	LPT 17963/04	Acute toxicity study of SPM 927 by single intravenous administration to CD-1 mice		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	8540	In vitro pharmacology: GABA transaminase assay		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	SCHW001	Evaluation of SPM 927 alone and in combination with clozapine on the prepulse inhibition of the startle response in C56/BL6 mice		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	04.270/3	Evaluation of SPM 927 in the behavioral despair test in the rat (i.p. administration)		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	AA19072	Effects of SPM 927 on reserpine-induced tardive dyskinesia in mice		
12-Sep-06	0285		Information Amendment: Pharmacology/Toxicology	Krishtal	Electrophysiological characterization of SPM-927		
15-Sep-06	0286		Initial Safety Report	SP774		2006-00366	104504
15-Sep-06	0287		Follow-up Safety Report	SP830		2006-00278	112204
15-Sep-06	0287		Follow-up Safety Report	SP745		2006-00357	175702
18-Sep-06			General Correspondence	SP903	Email Ms. Calder, FDA, to request she follow up with CSS about timeline for response to 28-AUG-2006 abuse liability protocol submission		
19-Sep-06			FDA Correspondence	SP903	Ms. Calder, FDA, emails that CSS has completed its review of the abuse liability protocol and will send comments soon		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
19-Sep-06			General Correspondence	SP903	Email Ms. Calder, FDA, thanks for following up with CSS on abuse liability protocol review		
20-Sep-06			General Correspondence	SP903	Email Ms. Calder, FDA, thanks for recommendations regarding the abuse liability protocol		
20-Sep-06			General Correspondence		Email Ms. Calder, FDA, for feedback on questions in cover letter of abuse liability submission		
20-Sep-06			FDA Correspondence	SP903	Ms. Calder, FDA, emails 'you're welcome' for recommendations regarding the abuse liability protocol		
20-Sep-06			FDA Correspondence	SP903	Ms. Calder, FDA, emails recommendations regarding the abuse liability protocol		
20-Sep-06	0288		Protocol Amendment: New Investigator	SP757	Revised investigator		
26-Sep-06	0289		7-Day Safety Report	SP745		2006-00389	170304
03-Oct-06			FDA Meeting Minutes		Ms. Calder, FDA, emails meeting minutes from 06-SEP-2006 meeting to discuss the electronic submission of multiple NDAs with multiple indications		
10-Oct-06	0290		Follow-up Safety Report	SP745		2006-00389	170304
16-Oct-06	0291		Initial Safety Report	SP874		2006-00403	125009/80029

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
16-Oct-06	0292		7-Day Safety Report	SP745		2005-00509	171324
19-Oct-06	0293		Initial Safety Report	SP774		2006-00409	122402
19-Oct-06	0294		Follow-up Safety Report	SP754		2005-00370	12804/80207
23-Oct-06	0295		7-Day Safety Report	SP830		2006-00420	105309
23-Oct-06	0296		General Correspondence	SP903	Submit Protocol SP903 integrating comments from CSS		
25-Oct-06	0297		7-Day Safety Report	SP874		2006-00418	124701/80223
26-Oct-06	0298		Follow-up Safety Report	SP745		2006-00350	101802
26-Oct-06	0299		Information Amendment: Clinical	SP755	A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (200 and 400mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization		
02-Nov-06	0300		Initial Safety Report	SP774		2006-00094	114109
02-Nov-06	0301		Follow-up Safety Report	SP774		2006-00409	122402
02-Nov-06	0301		Follow-up Safety Report	SP754		2006-00209	14312/80405
07-Nov-06	0302		Follow-up Safety Report	SP830		2006-00420	105309

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
09-Nov-06	0303		Follow-up Safety Report	SP830		2006-00278	112204
13-Nov-06	0304		Follow-up Safety Report	SP830		2006-00129	115104
13-Nov-06	0304		Follow-up Safety Report	SP874		2006-00418	124701/80223
15-Nov-06	0305		Follow-up Safety Report	SP830		2006-00438	105318
28-Nov-06	0306		Follow-up Safety Report	SP830		2006-00438	105318
28-Nov-06	0306		Follow-up Safety Report	SP874		2006-00403	125009/80029
28-Nov-06	0306		Follow-up Safety Report	SP874		2006-00418	124701/80223
05-Dec-06	0307		7-Day Safety Report	SP874		2006-00472	102205/80148
05-Dec-06	0308		SB Meeting Minutes		Submit minutes from 15-NOV-2006 Type A meeting		
06-Dec-06	0309		General Correspondence		Submit IDMC correspondence wherein IDMC informs Schwarz that lacosamide up to 600mg can be allowed in trials of subjects with diabetic peripheral neuropathy		
11-Dec-06	0310		7-Day Safety Report	SP874		2006-00478	129704/80308
19-Dec-06	0311		Initial Safety Report	SP830		2006-00495	114006
19-Dec-06	0312		Follow-up Safety Report	SP874		2006-00478	129704/80308

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	A45202	SPM 927: Effect on survival and reproduction of Daphnia magna in a semi-static test over three weeks		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	A45180	SPM 927: Toxic effects to zebra fish (Brachydanio rerio) in an early-life stage toxicity test		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	699/17	(14C)-SPM 927: Quantitative whole-body autoradiography following oral and intravenous administration to the pigmented rat		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	8540	In Vitro Pharmacology: GABA Transaminase Assay – Study of SPM 927		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	847	Structure proposal for polar metabolite		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	826	SPM 927: Metabolite profiling and identification in the mouse, rat and dog		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	699/48	A study of absorption, distribution, metabolism and excretion following oral and intravenous administration to the dog		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	699/46	A study of absorption, distribution, metabolism and excretion following oral administration to the mouse		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	699/47	SPM 927: A study of absorption and excretion following oral administration to the rat		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	Drommer	SPM 927 Light and electron microscopical investigation of liver tissues from study "13-week oral gavage subchronic toxicity of ADD 234037 in rats"		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	F9672	Evaluation of the neuroprotective efficacy of compound SPM 927 in rat hippocampal slice cultures after OGD, glutamate and staurosporine insult		
20-Dec-06	0313		Information Amendment: Pharmacology/Toxicology	865	Inhibition of the cytochrome P450 isoenzymes 1A1, 2A6, 2B6, 2C8, 2E1 and 3A5 by SPM 927 and SPM 12809		
21-Dec-06	0314		Initial Safety Report	SP774		2006-00481	112315
22-Dec-06	0315		Initial Safety Report	SP874		2006-00488	115902/80260
22-Dec-06	0316		Follow-up Safety Report	SP874		2006-00472	102205/80148
03-Jan-07	0317		Initial Safety Report	SP745		2006-00510	110718
03-Jan-07	0317		Initial Safety Report	SP615		2006-00515	10191
03-Jan-07	0318		Follow-up Safety Report	SP745		2006-00289	108305
03-Jan-07	0319		7-Day Safety Report	SP756		2006-00473	15606
17-Jan-07	0320		Initial Safety Report	SP774		2007-00013	116206
17-Jan-07	0321		Follow-up Safety Report	SP874		2006-00488	115902/80260

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
17-Jan-07	0321		Follow-up Safety Report	SP830		2006-00495	114006
17-Jan-07	0322		7-Day Safety Report	SP874		2007-00020	129506/80472
17-Jan-07	0322		7-Day Safety Report	SP874		2007-00023	115702/80415
24-Jan-07	0323		Information Amendment: Pharmacology/Toxicology	031209	Identification of harkoseride (SPM 927) targets using affinity capture and proteomics technologies		
24-Jan-07	0323		Information Amendment: Clinical	SP757	A multicenter, open-label trial to investigate the safety and tolerability of intravenous SPM 927 as replacement for oral SPM 927 in subjects with partial seizures with or without secondary generalization		
30-Jan-07	0324		Follow-up Safety Report	SP874		2007-00023	115702/80415
30-Jan-07	0324		Follow-up Safety Report	SP745		2006-00510	110718
30-Jan-07	0325		7-Day Safety Report	SP874		2006-00464	126603/80275
08-Feb-07	0326		Initial Safety Report	SP774		2007-00029	116205
12-Feb-07	0327		7-Day Safety Report	SP745		2007-00055	175516
12-Feb-07	0327		7-Day Safety Report	SP745		2007-00048	100806
12-Feb-07	0328		Follow-up Safety Report	SP874		2006-00464	126603/80275

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
12-Feb-07	0328		Follow-up Safety Report	SP615		2006-00515	2006-00515
20-Feb-07	0329		7-Day Safety Report	SP746		2007-00068	102802
20-Feb-07	0330		Initial Safety Report	SP745		2007-00061	108703
20-Feb-07	0330		Initial Safety Report	SP746		2007-00066	125012
20-Feb-07	0331		Follow-up Safety Report	SP874		2007-00020	129506/80472
23-Feb-07	0332		7-Day Safety Report	SP745		2007-00076	170801
23-Feb-07	0332		7-Day Safety Report	SP830		2007-00074	116001
23-Feb-07	0332		7-Day Safety Report	SP746		2007-00056	110804/80106
23-Feb-07	0333		Follow-up Safety Report	SP874		2006-00464	126603/80275
27-Feb-07	0334		Follow-up Safety Report	SP615		2003-00367	11776
27-Feb-07	0334		Follow-up Safety Report	SP746		2007-00068	102802
05-Mar-07	0335		Follow-up Safety Report	SP830		2007-00074	116001
12-Mar-07	0336		7-Day Safety Report	SP874		2007-00088	121012/80641

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
14-Mar-07	0337		Information Amendment: Clinical	SP640	A double-blind, single-site, randomized, placebo- and positive-controlled, parallel-design trial of the electrocardiographic effects of 400 and 800mg per day of lacosamide in healthy male and female subjects: a thorough QT trial		
19-Mar-07	0338		General Correspondence		Request comment on plan to submit integrated safety datasets for all patients in phase 2b/3 trials		
20-Mar-07	0339		Initial Safety Report	SP774		2006-00319	124611
20-Mar-07	0340		Follow-up Safety Report	SP830		2006-00420	105309
20-Mar-07	0340		Follow-up Safety Report	SP874		2006-00488	115902/80260
23-Mar-07	0341		General Correspondence	SP906	Updated cardiovascular safety report		
26-Mar-07	0342		7-Day Safety Report	SP874		2007-00100	101408/80363
26-Mar-07	0343		Follow-up Safety Report	SP746		2007-00066	125012
04-Apr-07	0344		Information Amendment: Pharmacology/Toxicology	IS-4-2311 Adden	Addendum to the study report: the early evaluation of anticonvulsant drugs		
04-Apr-07	0344		Information Amendment: Pharmacology/Toxicology	05.673/4	Evaluation of SPM 927 for abuse potential using an i.v. self-administration paradigm in the rat		
04-Apr-07	0344		Information Amendment: Pharmacology/Toxicology	C13703	The effects of lacosamide in an animal model for migraine		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
04-Apr-07	0344		Information Amendment: Pharmacology/Toxicology	Morrow	Harkoseride in pre-clinical animal models of pain		
04-Apr-07	0344		Information Amendment: Pharmacology/Toxicology	05.264/2	Pseudo-isobolographic evaluation in combination with 5 other analgesic substances using the formalin (late phase) test in the rat (i.p. administration)		
04-Apr-07	0344		Information Amendment: Pharmacology/Toxicology	05.237/5	Evaluation of SPM 927 as a discriminative stimulus in a drug discrimination procedure in the rat		
04-Apr-07	0344		Information Amendment: Pharmacology/Toxicology	/B-PDG-2006-52(	UV/VIS-absorption of O-desmethyl-lacosamide (SPM 12809)		
13-Apr-07	0345		Follow-up Safety Report	SP874		2007-00088	121012/80641
13-Apr-07	0345		Follow-up Safety Report	SP745		2007-00061	108703
17-Apr-07	0346		Response to FDA Request for Information	SP640	Submit SP640 data in response to 22-MARCH-2007 email request from Malandro		
23-Apr-07			7-Day Safety Report Fax	SP745		2005-00835	174203
23-Apr-07	0347		7-Day Safety Report	SP745		2005-00835	174203
23-Apr-07	0348		Initial Safety Report	SP756		2006-00422	17407
23-Apr-07	0349		Follow-up Safety Report	SP615		2003-00367	11776

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
24-Apr-07	0350		Information Amendment: Clinical	SP754	A multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of SPM 927 (400 and 600 mg/day) as adjunctive therapy in subjects with partial seizures with or without secondary generalization		
27-Apr-07			Safety Report Fax	SP830		2006-00098	115110
27-Apr-07	0351		7-Day Safety Report	SP830		2006-00098	115110
03-May-07	0352		Follow-up Safety Report	SP874		2007-00100	101408/80363
09-May-07	0353		Initial Safety Report	SP756		2007-00140	14308
09-May-07	0354		Follow-up Safety Report	SP830		2006-00098	115110
09-May-07	0354		Follow-up Safety Report	SP745		2006-00510	110718
09-May-07	0355		Information Amendment: Pharmacology/Toxicology	977	Metabolite turnover of SPM 927, SPM 6912 and SPM 12809 in S9 fractions obtained from male rat and human livers		
09-May-07	0355		Information Amendment: Pharmacology/Toxicology	1000	Profiling of polar metabolite		
16-May-07	0356		Request FDA Comment	raft, LPT 20614/(	Request for FDA review and comment and teleconference to discuss Division's response		
17-May-07	0357		General Correspondence	SP754, SP756	Submit follow up information in response to 04-MAY-2007 email from Lana Chen, FDA	000#5#2006-00422	17407

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
21-May-07			7-Day Safety Report Fax	SP745		2005-00463	176213
21-May-07	0358		7-Day Safety Report	SP745		2005-00463	176213
21-May-07	0359		Follow-up Safety Report	SP745		2006-00510	110718
22-May-07	0360		Follow-up Safety Report	SP756		2006-00442	17407
07-Jun-07	0361		7-Day Safety Report	SP745		2007-00155	109133
21-Jun-07			General Correspondence		Email Ms. Griffis, FDA, plan to submit one all-inclusive NDA under one NDA number		
22-Jun-07	0362		Initial Safety Report	SP874		2007-00119	124413/80424
25-Jun-07	0363		Annual Report		For the period 26-MAR-2006 through 25-MAR-2007		
27-Jun-07	0364		Information Amendment: Clinical	SP746 subtrial	A double-blind, randomized withdrawal of lacosamide in subjects with painful diabetic neuropathy - subtrial to SP746		
06-Jul-07	0365		7-Day Safety Report	SP746		2007-00199	124902
06-Jul-07	0366		Initial Safety Report	SP774		2007-00201	106404
06-Jul-07	0367		General Correspondence				
12-Jul-07	0368		Initial Safety Report	SP746		2007-00203	101208

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
13-Jul-07			FDA Phone Contact		Discuss proposed schematic of NDA/eCTD organization and obtain updated status of juvenile toxicology protocol review		
19-Jul-07	0369		7-Day Safety Report	SP746		2007-00214	105622
20-Jul-07	0370		Response to FDA Request for Information		Submit additional information request by Ms. Griffis regarding proposed trade name submission		
23-Jul-07			FDA Phone Contact		Ms. Griffis, FDA, called on behalf of DMETS to request additional information on trade name review submission		
23-Jul-07			FDA Correspondence		Ms. Griffis, FDA, emails comments from nonclinical team regarding draft protocol for juvenile dog toxicity study		
30-Jul-07	0371		7-Day Safety Report	SP830		2007-00230	105806
30-Jul-07	0372		Follow-up Safety Report	SP745		2005-00835	174203
06-Aug-07	0373		Follow-up Safety Report	SP830		2007-00074	116001
08-Aug-07	0374		Initial Safety Report	SP746		2007-00231	118301
14-Aug-07	0375		7-Day Safety Report	SP615		2005-00465	10477
15-Aug-07	0376		7-Day Safety Report	SP746		2007-00244	102717
15-Aug-07	0376		7-Day Safety Report	SP830		2007-00248	114211

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
15-Aug-07	0376		7-Day Safety Report	SP745		2007-00246	110907
20-Aug-07	0377		7-Day Safety Report	SP830		2005-00618	105019
21-Aug-07	0378		Initial Safety Report	SP774		2006-00066	124406
21-Aug-07	0379		Follow-up Safety Report	SP746		2007-00231	118301
21-Aug-07	0379		Follow-up Safety Report	SP746		2007-00199	124902
23-Aug-07	0380		Information Amendment: Clinical	SP903	Single-site, randomized, double-blind, placebo- and active comparator controlled single-dose crossover trial to evaluate the abuse potential of lacosamide in healthy subjects with a history of recreationaly CNS depressant use		
27-Aug-07	0381		Follow-up Safety Report	SP746		2007-00199	124902
27-Aug-07	0381		Follow-up Safety Report	SP746		2007-00244	102717
27-Aug-07	0381		Follow-up Safety Report	SP830		2007-00248	114211
28-Aug-07	0382		7-Day Safety Report	SP745		2007-00255	108222
04-Sep-07	0383		Follow-up Safety Report	SP746		2007-00203	101208
07-Sep-07	0384		7-Day Safety Report	SP745		2007-00265	102202
07-Sep-07	0385		Follow-up Safety Report	SP830		2007-00248	114211

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
07-Sep-07	0385		Follow-up Safety Report	SP830		2007-00248	105019
12-Sep-07	0386		Follow-up Safety Report	SP746		2007-00214	105622
12-Sep-07	0386		Follow-up Safety Report	SP830		2007-00248	114211
12-Sep-07	0386		Follow-up Safety Report	SP615		2005-00465	10477
04-Oct-07	0387		Initial Safety Report	SP746		2007-00281	101707
15-Oct-07	0388		7-Day Safety Report	SP615		2007-00289	10180
16-Oct-07	0389		Initial Safety Report	SP756		2007-00295	15405
19-Oct-07	0390		Initial Safety Report	SP745		2007-00288	114721
19-Oct-07	0391		Information Amendment: Clinical		Investigator's Brochure dated 31-AUG-2007		
25-Oct-07	0392		Initial Safety Report	SP615		2007-00292	11429
30-Oct-07	0393		Follow-up Safety Report	SP756		2007-00295	15405
01-Nov-07	0394		7-Day Safety Report	SP746		2007-00308	105621
01-Nov-07	0395		Initial Safety Report	SP774		2006-00439	100804
12-Nov-07	0396		Initial Safety Report	10053		2007-00316	SP615

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
14-Nov-07	0397		Initial Safety Report			2007-00317	101904
15-Nov-07	0398		General Correspondence		Appointment of UCB as agent in safety reporting to the IND		
04-Dec-07	0401		Follow-up Safety Report			2007-00316	10053
04-Dec-07	0402		Follow-up Safety Report			2007-00288	114721
05-Dec-07	0403		Protocol Amendment: New Protocol	SP925	Original Protocol		
20-Dec-07	0407		General Correspondence	LPT 20615	Request FDA concurrence on proposed dosing increase		
28-Feb-08			General Correspondence		Email Ms. Ware, FDA, proposed language for updating Informed Consent based on the FDA Alert for suicidality and antieleptic drugs		
20-Mar-08	0417		Protocol Amendment: New Investigator	SP925	New investigator		
01-Apr-08			General Correspondence		Email Ware that revised Informed Consent language will be distributed to all lacosamide INDs		
01-Apr-08			FDA Correspondence		Ware emails Division's response to proposed Informed Consent language		
20-May-08	0420		Protocol Amendment: New Investigator	SP925	New investigators		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	F-9945	Differential block of sensory neuronal voltage-gated sodium channels by lacosamide, lidocaine and carbamazepine. (Previously: Effect of lacosamide on recombinant Nav 1.3 and Nav 1.7 voltage-gated sodium current properties)		
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	LPT 20614/06	6-Week Dose-Range-Finding Study for a 33-Week Chronic Toxicity Study of SPM 927 by Repeated Oral Administration to Juvenile Beagle Dogs		
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	0699/069	(14C)-SPM 927: A study of absorption and excretion following single oral administration to the rabbit		
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	847 Amend 1	Structure proposal for polar metabolite		
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	9496	Oxford Cardiac Pharmacology Ltd: Effect of lacosamide on action potential parameters (including Vmax, the maximal rate of rise) in guinea pig ventricular myocytes		
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	MD-11-011-0012	Evaluation of potential effect of Lacosamide in the acute experimental allergic encephalomyelitis rat model		
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	F-9938	Effect of lacosamide on slow inactivation in Nav 1.2 (expressed in CHO cells) Nav 1.4 and Nav 1.4 and Nav 1.4/IFM>QQQ (expressed in Xenopus oocytes)		

Submission Date	Serial No	Location	Submission Type	Study No	Title/ Description	CIOMS Mfr Control No	CIOMS Subject No
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	SCHW 004	Evaluation of Lacosamide in an animal model for obsessive compulsive disorder: marble burying		
28-May-08	0422		Information Amendment: Pharmacology/Toxicology	F-9928	Determination of interaction of lacosamide with the antiepileptic drugs carbamazepine, Phenytoin, sodium valproate, lamotrigine, levetiracetam, topiramate and gabapentin		
24-Jun-08	0424		Annual Report		Period covering March 26, 2007 through March 25, 2008		
20-Aug-08	0425		Protocol Amendment: New Investigator	SP925	New investigators		
09-Oct-08	0431		Protocol Amendment: Change in Protocol	SP925	Amendment 1		

NDA 22-254 Submissions

Date	*Serial No*	*Submission Type*	*Study No*	*Title of Report*
28-Sep-07	0000	Original NDA		
20-Nov-07		FDA Correspondence		Ms. Ware, FDA, emails request from clinical pharmacology group related to initial filing review of the lacosamide applications
26-Nov-07	0001	Response to FDA Request for Inf		Submit response to 20-NOV-2007 clinical pharmacology request
10-Dec-07		FDA Correspondence		Dr. Katz, FDA, sends letter accepting NDA for filing
13-Dec-07		Amendment to a Pending Applicat		Submit additional clinical pharmacology responses
13-Dec-07	0002	Amendment to a Pending Applicat		Response to request: clinical pharmacology; provide responses not included in 0001
19-Dec-07		General Correspondence		Email Ms. Ware, FDA, preliminary responses to 74-day letter
07-Jan-08		FDA Correspondence		Ms. Ware, FDA, emails request from clinical and statistical team for additional datasets
07-Jan-08		General Correspondence		Email Ms. Ware, FDA, that requested datasets were sent on DVD via courier
14-Jan-08		FDA Correspondence		Ms. Ware, FDA, emails requests from DNP's clinical team related to ongoing review of lacosamide applications
15-Jan-08		General Correspondence		Email Ms. Ware, FDA, for additional explanation on clinical questions received 14-JAN-2008
15-Jan-08		FDA Correspondence		Ms. Ware, FDA, emails responses from email information request related to 14-JAN-2008 FDA email
16-Jan-08		General Correspondence		Email Ms. Ware, FDA, summary of 16-JAN-2008 conversation discussing GCP inspections
16-Jan-08		FDA Correspondence		Mr. Sullivan, FDA, emails outstanding clinical pharmacology items
17-Jan-08		FDA Correspondence		Ms. Gunther, FDA, emails information request for potential inspection sites
23-Jan-08	0003	Amendment to a Pending Applicat		120-day safety update and 74-day letter responses
29-Jan-08		FDA Correspondence		Ware emails request form DNP's clinical team for a summary table of AE that led to dose reduction and/or discontinuation by SOC and PT in Pool EP S1 by dose at onset

Date	*Serial No*	*Submission Type*	*Study No*	*Title of Report*
31-Jan-08		FDA Correspondence		Ms. Ware, FDA, emails request from DNP's clinical team
04-Feb-08		FDA Correspondence		Ms. Mercado, FDA, emails request for confirmation for FDA inspection of NDA 22-254 in Germany
06-Feb-08		FDA Correspondence	SP742, SP743, SP768	Sullivan emails request additional analyses for SP742, SP743, and SP768
07-Feb-08		FDA Correspondence		Sheryl Gunther, FDA, emails request for addresses for investigators Nischik, Pojakovic, and Hajnsek
08-Feb-08		General Correspondence		Email Ms. Gunther, FDA, contact information requested 07-FEB-2008
08-Feb-08		FDA Correspondence		Ms. Gunther, FDA, emails thanks for contact information
08-Feb-08		General Correspondence		Email Ms. Ware, FDA, partial responses to questions received 14-JAN-2008 and 31-JAN-2008
08-Feb-08		Response to FDA Request for Inf		Send Ms. Gunther, FDA, background investigator information rquested 17-JAN-2008
12-Feb-08		General Correspondence		Email Ms. Ware, FDA, additional partial responses to questions received 14-JAN-2008 and 31-JAN-2008
13-Feb-08	0004	Amendment to a Pending Applicat		Response to request: clinical; respond to questions received 15-JAN, 29-JAN, and 31-JAN-2008
14-Feb-08		FDA Correspondence		Ms. Ware, FDA, emails requests from DNP's clinical team
14-Feb-08		General Correspondence		Email Ms. Ware, FDA, that one request from 14-FEB-2008 email is addressed in lifecycle received today and the other will be reviewed
22-Feb-08		General Correspondence		Email Ms. Ware, FDA, responses to request from 14-FEB-2008 email
25-Feb-08	0005	Amendment to a Pending Applicat		Response to request: clinical; respond to 31-JAN-2008, 06-FEB-2008, and 14-FEB-2008 email requests
26-Feb-08		FDA Correspondence		Ms. Ware emails request from DNP's clinical pharmacology team
03-Mar-08		FDA Correspondence		Ms. Ware, FDA, emails requests from DNP's clinical team
05-Mar-08		FDA Correspondence		Email Ms. Ware, FDA, response to one of the request received 03-MAR-2008
05-Mar-08		General Correspondence		Email Ms. Ware, FDA, response to request received 26-FEB-2008

Date	Serial No	Submission Type	Study No	Title of Report
06-Mar-08		FDA Correspondence		Sullivan emails request from DAARP team for narratives for all patients with AEs of syncope of presyncope and tables comparing frequence of event by treatment group
07-Mar-08		FDA Correspondence	SP754	Ware emails requests from DNP's clinical team; request additional detail on subject 75411401 and clarification of footnote in cardiac report
07-Mar-08		FDA Phone Contact		Discuss NDA reviews with Ms. Ware, FDA
10-Mar-08		General Correspondence		Email Ms. Ware, FDA, clarification on 03-MAR-2008 request
10-Mar-08		Response to FDA Request for Inf		Submit requested ECG data for subjects in EP Pool S1
11-Mar-08		FDA Correspondence		Mr. Sullivan emails on behalf of Ms. Ware request for additional analyses
11-Mar-08		General Correspondence		Email Dr. Vallalba and Ms. Ware password for response to request for EP pool S! dataset from ISS
11-Mar-08		General Correspondence		Request Ms. Ware forward 11-MAR-2008 email to Dr. Vallalba
13-Mar-08		FDA Correspondence	SP903	Sullivan emails request from the stats reviewer for clarification on abuse liability study's dataset
20-Mar-08	0006	Amendment to a Pending Applicat		Response to Request: Clinical; respond to 04-MAR-2008 teleconference request and 13-MAR-2008 email; also respond to email requests 26-FEB-2008, 03-MA$-2008, 07-MAR-2008, 11-MAR-2008; provide draft blister labels and cartons requested in 74-day letter
20-Mar-08		FDA Correspondence		Sullivan emails CMC IR letter that applies to drug substance, tablet, and IV drug product
20-Mar-08		FDA Correspondence		Dr. Sood, FDA, mails information request letter regarding drug substance and drug product
31-Mar-08		FDA Correspondence		Sullivan emails request to resubmit ISS lab1.xpt and lab2.xpt datasets as separate files
02-Apr-08		FDA Correspondence		Ware emails requests from DNP's statistical team
03-Apr-08		FDA Correspondence		Ware emails requests from DNP's statistical team
03-Apr-08	0007	Amendment to a Pending Applicat		Response to Request: Clinical; respond to 07-MAR-2008 email request for clarification on subject 75411401 and 31-MAR-2008 email request for lab datasets
04-Apr-08		General Correspondence		Email Ware receipt of 04-APR-2008 comments regarding impurity specifications
04-Apr-08		General Correspondence		Email Ware agreement to be available 07-APR-2008 between 1pm and 3pm to discuss internal FDA meeting

Date	Serial No	Submission Type	Study No	Title of Report
04-Apr-08		FDA Correspondence		Ware emails that labeling submission next week is acceptable; would like to speak about updates from internal meeting
04-Apr-08		FDA Correspondence		Ware adds additional comment to email sent earlier today
04-Apr-08		FDA Correspondence		Ware emails comments from ONDQA and OND non-clinical review teams related to proposed impurity specifications
04-Apr-08		General Correspondence		Email Ware if there is any update regarding CSS and the tradename and notify that revised label/container cartons will be sent next week
07-Apr-08		FDA Correspondence		Ware emails agreement to clarification on symbol in 04-APR-2008 request
07-Apr-08		General Correspondence		Email Ware clarification on symbol in 04-APR-2008 request
09-Apr-08	0008	Amendment to a Pending Applicat		Revised labeling - excluding package insert
11-Apr-08		General Correspondence		Email Ware responses to 02-APR-2008 statistical questions
11-Apr-08		General Correspondence		Email Ware responses to questions emailed 04-APR-2008 on drug substance and IV/syrup formulation
14-Apr-08	0009	Amendment to a Pending Applicat		Response to Request: Clinical; respond to 06-MAR-2008 and 07-MAR-2008 clinical email requests for narratives for all neuropathic pain subjects with syncompe or presyncope; provide narratives for migraine study dropouts as requested in 11-MAR-2007 email
16-Apr-08		FDA Correspondence		Ware emails request from DNP's clinical team regarding overall exposure to lacosamide and placebo in all studies
18-Apr-08		Amendment to a Pending Applicat		Provide responses to requests in CMC letter dated 20-MAR-2008 and emails dated 02-APR-2008 and 04-APR-2008
18-Apr-08		FDA Correspondence	SP755, SP774, SP757	Ware emails request from DNP's clinical team regarding patients 170106 and 17011
18-Apr-08	0010	Amendment to a Pending Applicat		Respond to 20-MAR-2008 CMC request and 02-APR-2008 and 04-APR-2008 email requests
25-Apr-08		FDA Correspondence		Ware emails request from DNP's CMC review team
25-Apr-08		FDA Correspondence		Ware emails request from DNP's clinical team regarding subject 588/8061
28-Apr-08		General Correspondence		Email Ware Schwarz commitments following 23-APRIL-2008 teleconference regarding oral syrup dosing

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29-Apr-08		FDA Correspondence		Sullivan emails request for narratives of patients with AE dyskinesia
30-Apr-08	0011	Amendment to a Pending Applicat		Respond to requests received 20-MAR-2008, 16-APR-2008, and 18-APR-2008
30-Apr-08		Response to FDA Request for Inf	1106	Email Ware partial response to 25-APRIL-2008 email request regarding CMC data
06-May-08		FDA Correspondence		Sullivan emails request from reviewer of Environmental Assessment to submit a non-confidential EA
07-May-08		FDA Correspondence		Ware emails request from DNP's clinical team requesting narratives and CRFs for four patients who discontinued due to cardiac or ECG issues; ECGs for 755122303; suicidality information on 754/12512
08-May-08		Response to FDA Request for Inf		Email Ware dyskinesia narratives requested in 29-APRIL-2008 email
09-May-08	0012	Amendment to a Pending Applicat		Response to requests; respond to nonclinical question in 25-APR-2008 email and provide revision to environmental assessment requested in 06-MAY-2008 email
12-May-08		FDA Correspondence		Ware emails requests from DNP's clinical team
12-May-08		General Correspondence		Email Ware that 12-MAY-2008 requests have been received
12-May-08		FDA Correspondence		Ware emails request from chemistry review team regarding NDA 22-254 and NDA 22-255
13-May-08		Response to FDA Request for Inf		Email Ware AE report responding to 25-APRIL-2008 email request regarding subject 588-8061
13-May-08		General Correspondence		Email Ware requested laboratory results for subject 588/5061
16-May-08		Response to FDA Request for Inf		Email Ware response to questions 2, 3, and 4 from 12-MAY-2008 email request
16-May-08		Response to FDA Request for Inf		Email Ware responses to bullets 1 and 2 from 07-MAY-2008 email request regarding narratives and CRFs and ECG data
16-May-08		General Correspondence		Email Ware question/proposal regarding request number 5 from 12-MAY-2008 email request
16-May-08		FDA Correspondence		Ware emails request from clinical reviewer for clarification on tables EP 5.1.1 and EP 5.1.2 from partial response to 12-MAY-2008 request
19-May-08		Response to FDA Request for Inf		Email Ware partial response to 16-MAY-2008 email request and suggest teleconference if response is not sufficient
19-May-08		Response to FDA Request for Inf		Email Ware response to bullet 3 from 07-MAY-2008 email request regarding subject 754/12512 suicidality

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20-May-08		FDA Correspondence	SP643	Ware emails requests from clinical pharmacology review team regarding SP643 and analytical assay validation methods
21-May-08		FDA Correspondence		Ware emails WORD document of example table for requested summary information on analytical assay validation methods
22-May-08		FDA Correspondence		Ware emails request from clinical review team for additional information on subject 588/8061
23-May-08		General Correspondence		Email Ware response to 22-MAY-2008 request for information on subject 588/5061
23-May-08		Response to FDA Request for Inf		Email Ware response to email request received 22-MAY-2008 regarding subject 588/8061
27-May-08		Response to FDA Request for Inf	SP643	Email Ware responses to clinical pharmacology requests received in 20-MAY-2008 email regarding subject classification in SP643 and analytical assay validation methods
27-May-08	0013	Amendment to a Pending Applicat		Response to requests in 25-APR-2008, 29-APR-2008, 07-MAY-2008, 12-MAY-2008, 16-MAY-2008, and 22-MAY-2008 emails
30-May-08		FDA Phone Contact		Ware calls to request WORD copy of draft labeling; also discuss review items: scheduling, labels, post-marketing requests, REMS, pediatrics, class labeling
02-Jun-08		FDA Correspondence		Ware emails question about 02-JUNE-2008 response to 12-MAY-2008 question 1
04-Jun-08		General Correspondence		Email Ware concomitant disease tables requested 12-MAY-2008
06-Jun-08		FDA Correspondence		Ware emails request for teleconference 12-JUNE-2008 at 10:15 to discuss potential cases of multi-organ hypersensitivity
11-Jun-08	0014	Amendment to a Pending Applicat		Respond to requests received 12-MAY-2008 and 2-JUN-2008
11-Jun-08		FDA Correspondence	SP830	Ware emails request for additional information on subject SP830/111201 and request for database search for all cases of potential multiorgan hypersensitivity reactions
26-Jun-08		FDA Phone Contact		Ware calls to discuss review with goal of reaching an actio by 29-JUL-2008, dependent on review of multi-organ hypersensitivity data; also discuss labeling
30-Jun-08		Meeting Request		Type A meeting request to discuss abuse potential of lacosamide
02-Jul-08		FDA Correspondence		Ware emails comments from controlled substance staff with conclusion that lacosamide has abuse potential similar to alprazolam, a schedule IV drug
03-Jul-08		General Correspondence		Email Ware requested documents
10-Jul-08		General Correspondence		Email Ware response to multiorgan hypersensitivity issue raised in 06-JUN-2008 email, 11-JUN-2008 email, and 12-JUN-2008 teleconference

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10-Jul-08		General Correspondence		Email Sullivan to ask when to expect draft labeling from DAARP
11-Jul-08		General Correspondence		Email Ware pediatric development document
11-Jul-08	0015	Amendment to a Pending Applicat		Response to requests; respond to request in 11-JUN-2008 teleconference to search for cases of multi-organ hypersensitivity based on defined criteria; final part of response to 12-MAY-2008 CMC request; and Type A meeting request
12-Jul-08		Response to FDA Request for Inf		Email Ms. Ripper, FDA, table of enrollment and last subject dates in response to financial disclosure request
12-Jul-08		General Correspondence		Email Leah Ripper, FDA, table showing financial disclosure cutoff dates by trial.
14-Jul-08		FDA Correspondence		Ripper emails that financial disclosure information emailed 12-JUL-2008 addresses her concern
15-Jul-08		FDA Correspondence		Ware emails that DNP and DAARP labeling comments will likely be combined
15-Jul-08		General Correspondence		Ware emails that DAARP and DNP labeling comments will be combined
17-Jul-08	0016	Amendment to a Pending Applicat		Response to requests; provide case report forms related to 0015 submission
18-Jul-08		FDA Phone Contact		Teleconference to discuss multi-organ hypersensitivity and three month extension of review clock
21-Jul-08		General Correspondence		Email Ms. Ware request for copy of Eight Factor Analsis prepared by CSS to determine lacosamide's scheduling
21-Jul-08		General Correspondence		Email Ware request for copy of full Eight Factor Analysis prepared by CSS
22-Jul-08		General Correspondence		Email Ware requesting discussion on CSS analysis, potential extension of PDUFA date, clinical hold, and safety update
25-Jul-08		FDA Correspondence		Ware emails the Action letter for pain indication should be issued based on the old regulations
25-Jul-08		FDA Phone Contact		SB calls Ware to discuss additional terms for multiorgan hypersensitivity, extension of action date, CSS analysis, safety update, pediatric clinical hold, and draft label
25-Jul-08		General Correspondence		Email Sullivan to ask if Action letter for LCM for pain will be a Complete Response letter or the old style of approvable or not approvable
25-Jul-08		FDA Correspondence		Ware emails list of additional search terms suggestive or internal organ involvement
28-Jul-08		General Correspondence		Email Ware request from medical colleagues for clarity on inclusion of preferred terms hepatitis and hypersensitivity in multiorgan hypersensitivity analysis

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28-Jul-08		FDA Correspondence		Sare Stradley emails "Not Approvable" letter for 22-284
29-Jul-08		FDA Correspondence		Stradley emails that FDA will be in touch about scheduling meeting requested 29-JUL-2008
29-Jul-08		General Correspondence		Email Ware and Sullivan lifecycle 0017, response to 22-284 action letter received 28-JUL-2008, meeting request, and request for extension of review period
30-Jul-08	0017	Amendment to a Pending Applicat		Request for extension of review period; meeting request
30-Jul-08		General Correspondence		Email Ware supporting data for subject 588/8061 where the bilirubin value was normal
31-Jul-08		FDA Correspondence		Ware emails request for laboratory value critieria clarification
31-Jul-08		FDA Correspondence		Nighswander mails PDUFA extension letter for epilepsy indications
01-Aug-08		FDA Correspondence		Ware emails request from DNP's clinical team to clarify the denominators used in the search for potential multi-organ hypersensitivity
01-Aug-08	0018	Amendment to a Pending Applicat		Response to requests; provide proposed questions for Type A meeting requested 30-JUN-2008; provide location of CRF data for subject 588/8061; submit high level pediatric development plan
04-Aug-08		FDA Phone Contact		Stradley calls to discuss meeting on Not Approvable letter for the pain indication
06-Aug-08		FDA Correspondence		Sullivan emails that 22-284 meeting request is considered a Type A meeting but usually can't be granted in requested time frame
06-Aug-08		FDA Correspondence		Ware emails comments from Controlled Substance Staff in response to 31-JUL-2008 request
07-Aug-08		General Correspondence		Email Ware clarification question on CSS analysis
11-Aug-08		General Correspondence		Email Ware requesed normal lab values for subject 588/8061
14-Aug-08	0019	Amendment to a Pending Applicat		Response to requests; respond to 18-JUL2008 teleconference and 25-JUL and 31-JUL email requests for addition of search terms and criteria to multi-organ hypersensitivity search; provide normal lab values for subject 588/8061 as requested 31-JUL-2008
19-Aug-08		General Correspondence		Email Ware questions regarding meeting package to be sent for 29-SEP-2008 meeting
19-Aug-08		General Correspondence		Email Ware request for cardiac section of the draft label and question on pediatric drug development
21-Aug-08		General Correspondence		Email Ware response to 01-AUG-2008 request for multi-organ hypersensitivity information

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21-Aug-08		FDA Phone Contact		Discussion of meeting with DNP/CSS on scheduling and to discuss responses to questions previously asked
27-Aug-08	0020	Amendment to a Pending Applicat		Response to requests; respond to 01-AUG-2008 email request for clarification on multi-organ hypersensitivity reaction denominators; provide revised blister labels
04-Sep-08	0021	Meeting Package		Information package for Type A meeting on September 29, 2008
10-Sep-08		General Correspondence		Email Ware that response to multi-organ hypersensitivity request was sent as life cycle 19 on 14-AUG-2008
23-Sep-08	0022	Amendment to a Pending Applicat		Meeting Package for Type A meeting on October 16, 2008
26-Sep-08		General Correspondence		Email Sullivan letter from Schwarz to EMEA withdrawing the lacosamide pain application
26-Sep-08		FDA Correspondence		Ware emails Agency's preliminary responses to questions for 29-SEP-2008 meeting
29-Sep-08		FDA Correspondence		Sullivan emails that 15 desk copies will be required for 16-OCT-2008 meeting package
30-Sep-08		General Correspondence		Email Sullivan that meeting package for 16-OCT-2008 meeting will be sent via email today and as a lifecycle tomorrow, 01-OCT-2008
01-Oct-08		FDA Correspondence		Sullivan emails thanks for PDF of 16-OCT-2008 meeting package and provides mailing address for desk copies
03-Oct-08		FDA Correspondence		Ware emails list of FDA attendees from 29-SEP-2008 meeting
08-Oct-08		General Correspondence		Email Ware meeting minutes and meeting slides from 29-SEP-2008 meeting with DNP and CSS
10-Oct-08		General Correspondence		Email Ware letter from Patty Fritz requesting teleconference to discuss scheduling
14-Oct-08		FDA Correspondence		Dr. Throckmorton emails to notify that Agency is discussing how best to handle teleconference requested 10-OCT-2008
15-Oct-08	0023	Amendment to a Pending Applicat		Reply to FDA preliminary response to questions submitted in life cycle 0021 concerning CSS recommendations of C-IV scheduling
15-Oct-08	0023	Amendment to a Pending Applicat		Reply to FDA preliminary response to questions submitted in life cycle 0021 concerning CSS recommendations of C-IV scheduling
17-Oct-08		General Correspondence		Email Ware proposed REMS form
21-Oct-08		FDA Phone Contact		Ware returned call to discuss isses from label review, including storage conditions, safety pharmacology section, CSS class, suicidality, and post-marketing commitments

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21-Oct-08	0024	Amendment to a Pending Applicat		Proposed REMS
21-Oct-08	0024	Amendment to a Pending Applicat		Proposed REMS
23-Oct-08		FDA Correspondence		Ware emails post-marketing commitments and labeling revisions
23-Oct-08		General Correspondence		Email Ware response to Division label changes and proposals for consideration as well as a justification document for the sponsor-requested changes
27-Oct-08		General Correspondence		Email Ware analysis requested at 27-OCT-2008 meeting for PR outliers
29-Oct-08		FDA Correspondence		Ware emails complete response letter for 22-255 and approval letter for 22-253 and 22-254
30-Oct-08	0025	Amendment to a Pending Applicat	SP903	Response to request; additional information requested in 20-OCT-2008 teleconference by Dr. Throckmorton from SP903, abuse liability trial
30-Oct-08	0025	Amendment to a Pending Applicat	SP903	Response to request; additional information requested in 20-OCT-2008 teleconference by Dr. Throckmorton from SP903, abuse liability trial